GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF FOOD ALLERGY

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SECTION 1 INTRODUCTION

1.1 OVERVIEW

Food allergy is an important public health problem that affects adults and children and may be increasing in prevalence. Despite the risk of severe allergic reactions and even death, there is no current treatment other than allergen avoidance and treating the symptoms associated with severe reactions. Moreover, the diagnosis of food allergy may be problematic given that non-allergic food reactions, such as food intolerance, are frequently confused with food allergies. Additional concerns relate to the differences in the diagnosis and management of food allergy in different clinical practice settings.

Due to these concerns, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, working with more than 30 professional organizations, Federal agencies, and patient advocacy groups, led the development of "best practice" clinical guidelines for the diagnosis and management of food allergy, henceforth referred to as the Guidelines. Based on a comprehensive review and objective evaluation of the recent scientific and clinical literature on food allergy, the Guidelines were developed by and designed for allergists and clinical researchers and practitioners in the areas of pediatrics, family medicine, dermatology, gastroenterology, emergency medicine, pulmonary and critical care medicine, and others.

The Guidelines focus on diseases that are defined as food allergy (see Section 2.1), and include both immunoglobulin E (IgE)-mediated reactions to food and some non-IgE-mediated reactions to food. The Guidelines do not discuss celiac disease, which is an immunologic non-IgE-mediated reaction to certain foods. Although this is an important immune-based disease involving food, existing clinical guidelines for celiac disease will not be restated here.[1, 2]

In summary, the Guidelines

- Provide concise recommendations to a wide variety of healthcare providers on how to diagnose food allergy, manage ongoing food allergy, and treat acute food allergy reactions.
- Identify gaps in the current scientific knowledge to be addressed through future research.
- Identify and provide guidance on points of current controversy in patient management.

Finally, these Guidelines do not address the management of food-allergic patients outside of clinical care settings (e.g., schools and restaurants) or the related public health policy issues. These issues are beyond the scope of this document.

1.2 HOW THE GUIDELINES WERE DEVELOPED

1.2.1 THE COORDINATING COMMITTEE

NIAID established a Coordinating Committee (CC), whose members are listed in Appendix A, to oversee the development of the Guidelines, review the draft Guidelines, and approve the final Guidelines. The CC was also responsible for the review of drafts for accuracy, practicality, clarity, and broad utility of the recommendations in clinical practice. The CC members were professional organizations, advocacy groups, and Federal agencies, each of which appointed one or more representatives to serve on the Committee. Each organization, group, or agency had a single vote on the CC. Each representative was vetted for financial conflict of interest (COI) by NIAID staff. Potential COIs were posted on the NIAID Web site http://www3.niaid.nih.gov/topics/foodAllergy/clinical/Who/ExpertPanel/disclosure.htm.

1.2.2 THE EXPERT PANEL

The CC convened an Expert Panel (EP) in March of 2009 that was chaired by Joshua Boyce, MD (Brigham and Women's Hospital, Boston, MA). Panel members were specialists from a variety of relevant clinical, scientific, and public health areas (see Appendix B). Each member was vetted for financial COI by NIAID staff and approved by the CC. Potential COIs were posted on the NIAID Web site provided in Section 1.2.1.

The charge to the EP was to use an independent, systematic literature review (see Section 1.2.3), in conjunction with consensus expert opinion and EP-identified supplementary documents, to develop guidelines that provide a comprehensive approach for diagnosing and managing food allergy based on current state-of-the-science.

The EP organized the Guidelines into five major topic areas:

1. Definitions, prevalence and epidemiology of food allergy
2. Natural history of food allergy and associated disorders
3. Diagnosis of food allergy
4. Management of non-acute food allergic reactions and prevention of food allergy
5. Diagnosis and management of food-induced anaphylaxis and other acute allergic reactions to foods

Subtopics were developed for each of these five broad categories.

1.2.3 THE INDEPENDENT, SYSTEMATIC LITERATURE REVIEW AND REPORT

RAND Corporation prepared an independent, systematic literature review and evidence report on the state of science in food allergy. RAND Corporation had responded to the NIAID Request For Proposal AI2008035, "Systematic Literature Review and Evidence Based Report on Food Allergy," and was subsequently awarded the contract in September, 2008. The contract's Principal Investigator was Paul G. Shekelle, MD, PhD, an internationally recognized expert in the fields of practice guidelines and meta-analysis.

NIAID and the EP developed an extensive set of key questions, which were further refined in discussions with the RAND Corporation. Literature searches were performed on PubMed, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and the World Allergy Organization Journal, one relevant journal that is not included in PubMed. In most cases, searches were limited to the years 1988 to the present, with no language restrictions. Additional publications identified by the EP and others involved in the review process were also included in the RAND review if and only if they met the RAND criteria for inclusion.

RAND researchers screened all titles found through searches, or that were submitted by the EP or NIAID. Screening criteria were established to facilitate the identification of articles concerning definitions, diagnoses, prevention, treatment, management, and other topics. Articles were included or excluded based on article type and study purpose as follows:

- Article type
  - Included: original research or systematic reviews
  - Excluded: background or contextual reviews; non-systematic reviews; commentary; other types of articles
- Study purpose
  - Included: incidence/prevalence/natural history; diagnosis; treatment/management/prevention
  - Excluded: not about food allergy; about some aspect not listed in the "included" category

RAND screened over 12,300 titles, reviewed over 1,200 articles, abstracted nearly 900 articles, and included more than 200 articles in the final RAND report. Two RAND investigators independently reviewed all titles and abstracts to identify potentially relevant articles. Articles that met inclusion criteria were independently abstracted by a single RAND investigator. Because of the large number of articles and the short time for the review, articles were not independently abstracted by two RAND investigators (dual-abstracted). However, team members worked together closely and data were double-checked. A concise version of the report will be published in a peer-reviewed journal and the full version of the report with a complete list of references will be made available to the public shortly afterwards.

1.2.4 ASSESSING THE QUALITY AND STRENGTH OF THE BODY OF EVIDENCE

For each key question, in addition to assessing the quality of each of the included studies, RAND assessed the quality of the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which was developed in 2004. GRADE provides a comprehensive and transparent methodology for grading the quality of evidence and strength of recommendations about the diagnosis, treatment, and management of patients. Using the GRADE approach, RAND assessed the

overall quality of evidence for outcomes and assigned a grade of evidence across outcomes according to the following criteria:[3,4]

- **High** = Further research is very unlikely to change our confidence on the estimate of effect.
- **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very Low** = Any estimate of effect is very uncertain.

RAND found that many of the topics searched did not have an extensive published literature and that many of these few published papers described small, observational studies rather than larger randomized clinical trials (RCT). This reflects a general paucity of published peer-reviewed studies, especially large RCT, in the field of food allergy. The designation of "Low" is not meant to imply that a paper is not factually correct or lacks scientific merit, but that it fails to meet objective criteria, such as study size and the use of placebo-controlled double-blind study design. It should be noted that the EP recommendations made in these Guidelines are often based on a GRADE classification of "Low", thus necessitating more contribution to the recommendation from expert opinion.

1.2.5 PREPARATION OF DRAFT GUIDELINES AND EXPERT PANEL DELIBERATIONS

The EP prepared a draft version of the Guidelines based on the RAND report and supplementary documents identified by the EP but not included in the RAND report. These documents contained information of significant value that was not well represented in the systematic literature review due to the objective criteria for inclusion or exclusion established by RAND, such as limits on demographics, study population size, and study design.

The EP used these supplementary documents only to clarify and refine conclusions drawn from sources in the systematic literature review. These documents are denoted in each of the Guideline section's bibliographies using an asterisk (*). It should also be noted that each section's bibliographies include references that are illustrative of the data and conclusions discussed, and do not represent the totality of relevant references. For a full list of relevant references, the reader should refer to the full version of the RAND report.

In October 2009, the EP discussed the first written draft version of the Guidelines and their recommendations. Following the meeting, the EP incorporated any panel-wide changes to the recommendations into the draft Guidelines. These revised recommendations were then subject to an initial panel-wide vote to identify where panel agreement was less than 90 percent. Controversial recommendations were discussed via teleconference and email to ensure group consensus. Following discussion and revision as necessary, a second vote was held. All recommendations that received 90 percent or higher agreement were included in the draft Guidelines for public review and comment. Recommendations that did not achieve 90 percent consensus at that time were no longer

considered recommendations and the text was revised to indicate that the EP failed to reach consensus when the draft Guidelines were released for public review and comment.

1.2.6 PUBLIC COMMENT PERIOD AND DRAFT GUIDELINES REVISION

The draft Guidelines were posted to the NIAID Web site in February of 2010 for a period of 60 days to allow for public review and comment. These comments were collected and reviewed by the CC and the EP, and some comments were then used to revise the Guidelines.

1.2.7 DISSEMINATION OF THE FINAL GUIDELINES

The final Guidelines were reviewed by the CC and, after a vote of approval, were posted to the NIAID Web site.

1.3 KEY DEFINITIONS AND ASSUMPTIONS

Within the Guidelines, the following terms and phrases are defined:

- "**Recommendation**" and "**Recommend**" are used when the EP **strongly** recommended for or against a particular course of action.
- "**Suggestion**" and "**Suggest**" are used when the EP **weakly** recommended for or against a particular course of action.

1.4 SUMMARY

The Guidelines, approved by the CC, present recommendations by an independent EP for the diagnosis and management of food allergy. They are intended to assist healthcare providers in making appropriate decisions about patient care. The recommendations are not fixed protocols that must be followed. Clinical judgment on the management of individual patients remains paramount. Clinicians, patients, and their families need to develop individual treatment plans that are tailored to the specific needs and circumstances of the patient. This document is intended as a resource to guide clinical practice and develop educational materials for patients, their families, and the public. It is not an official regulatory document of any Government agency.

1.5 REFERENCES

1. *Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, Hoffenberg EJ, Horvath K, Murray JA, Pivor M, Seidman EG. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroeneterol Nutr.* 2005; 40(1):1–19.
2. *Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. *Gastroenterology*. 2006; 131(6):1981–2002.

3. Shunemann A, Oxman A, Brozek J, Glasziou P, Jaeschke R, Vist GE, Williams JW Jr, KunzR, Craig J, Montori VM, Bossuyt P, Guyatt GH. GRADE Working Group: Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ.* 2008; 336:1106–10.
4. ***** Brozek JL, Akl EA, Jaeschke R, Lang DM, Bossuyt P, Glasziou P, Helfand M, Ueffing E, Alonso-Coello P, Meerpohl J, Phillips B, Horvath AR, Bousquet J, Guyatt GH, Schünemann HJ; GRADE Working Group. Grading quality of evidence and strength of recommendations in clinical practice guidelines: Part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies. *Allergy*. 2009; 64:1109–16.

***Supplementary document identified by the EP**

SECTION 2 DEFINITIONS, PREVALENCE, AND EPIDEMIOLOGY OF FOOD ALLERGY

2.1 DEFINITIONS OF FOOD ALLERGY, FOOD, AND FOOD ALLERGENS

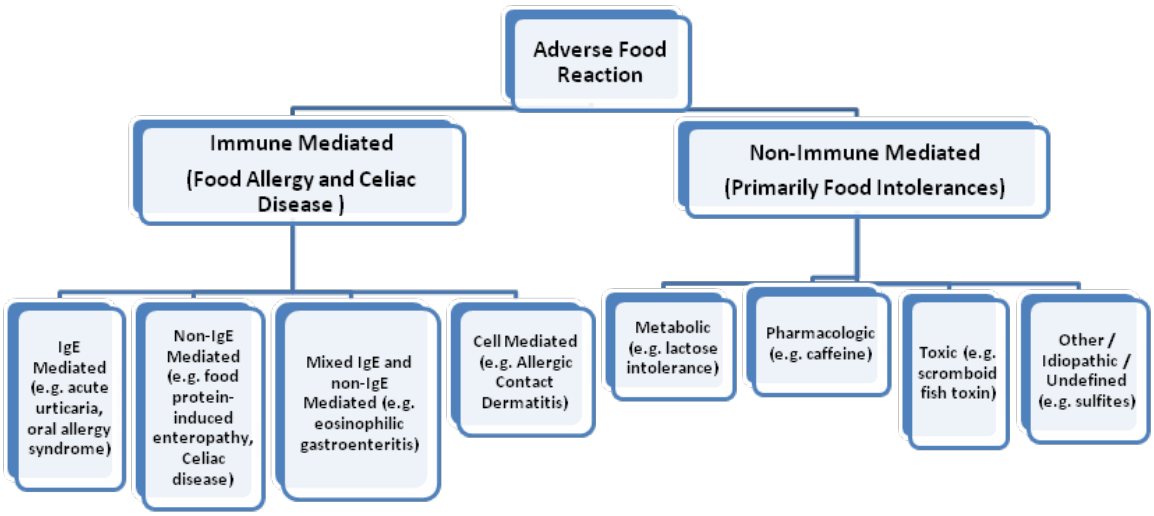
The Expert Panel (EP) came to consensus on definitions used throughout the Guidelines.

- A **food allergy** (FA) is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.
- A **food** is defined as any substance, whether processed, semi-processed or raw, which is intended for human consumption, and includes drinks, chewing gum, food additives, and dietary supplements. Substances used only as drugs, tobacco products, and cosmetics such as lip-care products that may be ingested are not included.
- **Food allergens** are defined as those specific components of food or ingredients within food (typically proteins, but sometimes also chemical haptens) that are recognized by allergen-specific immune cells and elicit specific immunologic reactions resulting in characteristic symptoms. Some allergens (most often from fruits and vegetables) cause allergic reactions primarily if eaten when raw. However, most food allergens can still cause reactions even after they have been cooked or have undergone digestion in the intestines. In some cases, food allergens may share structural or sequence similarity with other allergens, including aeroallergens; thus the adverse reaction may be caused by cross-reaction to the other allergen.

Although many different foods and food components have been recognized as food allergens,[1] these Guidelines focus only on those foods that are responsible for the majority of observed adverse allergic or immunologic reactions. Moreover, foods or food components that elicit reproducible adverse reactions but do not have established or likely immunologic mechanisms are not considered food allergens. These non-immunologic adverse reactions are instead termed **food intolerances**. For example, an individual may be allergic to milk due to an immunologic response to milk protein, or intolerant of milk due to an inability to digest lactose. Thus, milk protein is an allergen that triggers an adverse immunologic reaction. Lactose induces excess fluid in the GI tract resulting in abdominal pain and diarrhea because it is not metabolized, and is therefore not an allergen.

Adverse reactions to food can therefore be best categorized as those involving immunologic or non-immunologic mechanisms as summarized in Figure 2.1.

Figure 2.1: Types of adverse reactions to food



Non-immunologic reactions (food intolerances) can include metabolic, pharmacologic, toxic, and/or undefined mechanisms. In some cases, these reactions may mimic reactions typical of an immunologic response; it is therefore important to keep these food components or mechanisms in mind when evaluating adverse food reactions. Most adverse reactions to food additives, such as artificial colors (e.g., FD&C yellow 5 (tartrazine)) and various preservatives (e.g., sulfites), have no defined immunologic mechanisms; as a result, these food components, as well as other foods contributing to food intolerances, are not specifically discussed in these Guidelines.

The terms **allergy** and **allergic disease** are broadly encompassing and include clinical conditions associated with altered immunologic reactivity that may be either IgE mediated or non-IgE mediated.

The term **food hypersensitivity** is also often used to describe FA, although other groups have used this term more broadly to describe all other food reactions, including food intolerances. In these Guidelines, the EP has refrained from using the term "food hypersensitivity" except for the term "immediate gastrointestinal hypersensitivity," which is IgE mediated.

Because individuals can develop immunologic sensitization (as evidenced by the presence of allergen-specific IgE (sIgE)) to food allergens without having clinical symptoms on exposure to those foods, an sIgE-mediated FA requires **both** the presence of sensitization **and** the development of specific signs and symptoms on exposure to that food. Sensitization alone is not sufficient to define FA.

Although FA is most often caused by sIgE-mediated reactions to food, the EP also considered literature relevant to reactions likely mediated by immunologic but non-IgE-induced mechanisms (including food protein-induced enteropathy, exacerbations of eosinophilic gastrointestinal disorders (esophagitis, enteritis, colitis and proctitis), and

food-induced allergic contact dermatitis). In these conditions, sensitization to food protein cannot be demonstrated based on sIgE. The diagnosis of non-IgE-mediated FA is based on signs and symptoms occurring reproducibly on exposure to food, resolution of those signs and symptoms with specific food avoidance, and, most often, histologic evidence of an immunologically mediated process, such as eosinophilic inflammation of the gastrointestinal tract.

These Guidelines generally use the term "**tolerate"** to denote a condition where an individual has either naturally outgrown a FA, or has received therapy and no longer develops clinical symptoms following ingestion of the food. This ability to tolerate food does not distinguish two possible clinical states. Individuals may be tolerant only for a short term, perhaps because they have been desensitized by exposure to the food. Alternatively, they may develop long-term tolerance. The immunological mechanisms that underlie these two states are likely to be distinct. Thus, these Guidelines use the specific term "**tolerance**" only when they mean that the individual is clinically and immunologically tolerant to the food. Tolerance is actually a clinical definition, because immunologic tolerance in human food allergy is not fully defined. Tolerance means that the individual is symptom free upon food challenge weeks, months or years after the cessation of treatment and/or regular consumption of the food.

2.2 DEFINITIONS OF SPECIFIC FOOD ALLERGIC CONDITIONS

A number of specific clinical syndromes may occur as a result of FA and their definitions are as follows:

- **Food-induced anaphylaxis** is an IgE-mediated, rapid-onset, potentially life-threatening systemic reaction in which the affected individual may experience cardiovascular shock and/or serious respiratory compromise due to airway obstruction or bronchoconstriction.[2,3]
- **Gastrointestinal food allergies** include a spectrum of disorders that result from adverse immunologic responses to dietary antigens. Although there may be significant overlap between these conditions, several specific syndromes have been described. These are defined as follows:
  - **Immediate gastrointestinal hypersensitivity** refers to an IgE-mediated FA in which upper gastrointestinal (GI) symptoms may occur within minutes and lower GI symptoms may occur either immediately or with a delay of up to several hours.[4,5] This is commonly seen as a manifestation of anaphylaxis. Among the GI conditions, acute immediate vomiting is the most common reaction and perhaps the one best documented as immunologic and IgE mediated.
  - **Eosinophilic esophagitis** (EoE) involves localized eosinophilic inflammation of the esophagus.[6-8] While EoE is commonly associated with the presence of food-specific IgE, the precise causal role of FA in its etiology is not well defined. Both IgE- and non-IgE-mediated mechanisms seem to be involved based on the facts that food avoidance frequently leads to resolution, and that the responsible foods cannot always be identified by IgE testing. In children,

EoE is responsible for feeding disorders, vomiting, reflux symptoms, and abdominal pain. In adolescents and adults it most often presents with dysphagia and esophageal food impactions.

- **Eosinophilic gastroenteritis (EG)** also is both IgE- and non-IgE-mediated, and commonly linked to food allergies.[5] EG describes a constellation of symptoms that vary depending on the portion of the GI tract involved and a pathologic infiltration of the GI tract by eosinophils that may be quite localized or very widespread.
- **Dietary protein-induced proctitis/proctocolitis** typically presents in infants who seem generally healthy but have visible specks or streaks of blood mixed with mucus in the stool.[5] IgE to specific foods is generally absent. The lack of systemic symptoms, vomiting, diarrhea, and growth failure help to differentiate this disorder from other gastrointestinal food allergies that present with similar stool patterns. Because there are no specific diagnostic laboratory tests, the causal role of food allergens such as those found in cow's milk or soy are inferred from a characteristic history on exposure. Many infants present while being breastfed, presumably as a result of maternally-ingested proteins excreted in breast milk.
- **Food protein-induced enterocolitis syndrome** (FPIES) is another non-IgE-mediated disorder presenting in infancy with vomiting and diarrhea severe enough to cause dehydration and shock.[5,9] Cow's milk and soy protein are the most common causes, although some studies also report reactions to other foods, including rice, oat, or other cereal grains. A similar condition has also been reported in adults, most often related to crustacean shellfish ingestion.
- **Oral allergy syndrome** (OAS), also referred to as pollen-associated FA syndrome, is a form of localized IgE-mediated allergy, usually to fresh fruits or vegetables, confined to the lips, mouth, and throat. OAS most commonly affects patients who are allergic to pollens. Symptoms include itching of the lips, tongue, roof of the mouth, and throat, with or without swelling, and/or tingling of the lips, tongue, roof of the mouth, and throat.

- **Cutaneous** reactions to foods are some of the most common presentations of FA and include IgE-mediated (urticaria, angioedema, flushing, pruritus), cell-mediated (contact dermatitis, dermatitis herpetiformis), and mixed IgE- and cell-mediated (atopic dermatitis) reactions. These are defined as follows:
  - **Acute urticaria** is a common manifestation of IgE-mediated FA, although FA is not the most common cause of acute urticaria and is rarely a cause of chronic urticaria.[10] Lesions develop rapidly after ingesting the problem food and appear as polymorphic, round or irregularly shaped pruritic wheals, ranging in size from a few millimeters to several centimeters.
  - **Angioedema** most often occurs in combination with urticaria and, if food induced, is typically IgE mediated. It is characterized by nonpitting, nonpruritic, well-defined edematous swelling that involves subcutaneous tissues (e.g., face, hands, buttocks, and genitals), abdominal organs, or the upper airway (i.e., larynx).[10] Laryngeal angioedema is a medical emergency

requiring prompt assessment. Both acute angioedema and urticaria are common features of anaphylaxis.

- **Atopic dermatitis/atopic eczema (AD)** is linked to a complex interaction between skin barrier dysfunction and environmental factors such as irritants, microbes, and allergens.[11] Null mutations of the skin barrier protein filaggrin may increase the risk for transcutaneous allergen sensitization and to the development of FA in subjects with AD.[12–14] The role of food allergy in the pathogenesis of these conditions remains controversial.[15] In some sensitized patients, particularly infants and young children, food allergens can induce urticarial lesions, itching, and eczematous flares, all of which may aggravate AD.[10]
- **Allergic contact dermatitis** is a form of eczema caused by cell-mediated allergic reactions to chemical haptens present in some foods, either naturally (e.g., mango) or as additives.[16] Clinical features include marked pruritus, erythema, papules, vesicles, and edema.
- **Contact urticaria** can be either immunologic (IgE-mediated reactions to proteins) or non-immunologic (caused by direct histamine release).

- **Respiratory manifestations** of IgE-mediated FA are important components of anaphylaxis but are uncommon in isolation.[17] This is true for both upper (rhinitis) and lower (asthma) respiratory symptoms.

2.3 PREVALENCE AND EPIDEMIOLOGY OF FOOD ALLERGY

The true prevalence of FA has been difficult to establish for several reasons.

- Although over 170 foods have been reported to cause IgE-mediated reactions, most prevalence studies have focused only on the most common food allergens.
- There may have been changes in the incidence and prevalence of FA over time, and many studies have indeed suggested a true rise in prevalence over the past 10 to 20 years.[18,19]
- Studies of FA incidence, prevalence, and natural history are difficult to compare due to inconsistencies and deficiencies in study design and variations in the definition of FA. These Guidelines do not exclude studies based on the diagnostic criteria used but the results must be viewed critically based on these diagnostic differences. In addition, studies from the United States and Canada are the focus of this report, but key studies from elsewhere are also included.

2.3.1 SYSTEMATIC REVIEWS OF THE PREVALENCE OF FOOD ALLERGY

- Two systematic reviews/meta-analyses on the prevalence of FA have recently been published.[20,21]
  - The paper by Rona et al.,[20] which includes data from 51 publications, stratifies to adults and children and provides separate analyses for the prevalence of food FA for five foods: cow's milk, hen's egg, peanut, fish, and crustacean shellfish. As shown in Table 2.1 below, the investigators report a pooled overall prevalence of self-reported food allergy of 13 percent and 12 percent

for adults and children, respectively, to any of these five foods. Pooled results are far lower (about 3 percent), however, when assessed by sensitization alone, sensitization with symptoms, or by double-blind, placebo-controlled food challenge. These data emphasize the fact that food allergies are over-reported by patients and that objective measurements are necessary to establish a true FA diagnosis. For specific foods, pooled results show that prevalence is highest for milk (3 percent by symptoms alone, 0.6 percent for symptoms plus positive skin prick test (SPT), and 0.9 percent for symptoms plus food challenge).

Table 2.1: Prevalence of allergy to peanut, milk, egg, fish, and crustacean shellfish[20]

Diagnostic Criteria	Overall prevalence	Peanut	Milk	Egg	Fish	Crustacean Shellfish
Self-reported symptoms: Children	12%					
Self-reported symptoms: Adults	13%					
Self-reported symptoms: All Ages		0.6%	3%*	1%	0.6%	1.2%
Symptoms plus skin test or serum IgE: All Ages	3%	0.75%	0.6%	0.9%	0.2%	0.6%
Food Challenge: All ages	3%	NE	0.9%	0.3%	0.3%	NE†

*Greater prevalence in children than adults, not specifically estimated but it appears to be about 6–7% in children and 1–2% in adults.
†NE: Not estimated

- The paper by Zuidmeer et al.,[21] which includes data from 33 publications, presents an epidemiological data review for fruits, vegetables/legumes, tree nuts, wheat, and soy. The results, summarized in Table 2.2 below, demonstrate that the reported prevalence for these foods is generally lower than for the five foods reported in Table 2.1. Once again, the prevalence of FA was much higher when assessed using self-reporting than when using sensitization or food challenge.

Table 2.2: Prevalence of allergy to fruits, vegetables/non-peanut legumes, tree nuts, wheat, and soy[21]

Diagnostic Criteria	Fruits	Vegetables / Non-Peanut Legumes	Tree Nuts	Wheat	Soy
Self-reported Symptoms	0.02–8.5%	0.01–13.7%	0–4.1%	0.2–1.3%	0–0.6%
Skin Test	0.02–4.2%	0.01–2.7%	0.04–4.5%	0.2–1.2%	0.03–0.2%
Challenge test	0.1–4.3%	0.1–0.3%	0.1–4.3%	0–0.5%	0–0.7%
Meta-analysis: Adult Studies	1.22% (symptoms)	0.1% (symptoms)	NE†	0.4% (symptoms) 2% (sensitization)	NE
Meta-analysis: Children Studies	NE	NE	0.5% (symptoms)	0.4% (sensitization)	NE

†NE: Not estimated

- The Center for Disease Control and Prevention (CDC) reviewed the International Classification of Diseases (ICD) codes in the US for food allergy in 2007 and found that approximately 3 million children under age 18 years (3.9 percent) reported a FA in the previous 12 months. From 2004 to 2006, this review noted that there were approximately 9,500 hospital discharges per year with a diagnosis related to FA among children under age 18 years.[18]
- Another US study analyzed national data from the Infant Feeding Practices Study II, a longitudinal mail survey from 2005 to 2007 of pregnant women who gave birth to a healthy single child of at least 35 weeks duration, beginning in the third trimester of pregnancy and periodically thereafter up to age 1 of the infant.[22] In this analysis, probable FA was defined as a doctor-diagnosed FA, or food-related symptoms of swollen eyes or lips or hives. Of 2,441 mothers, 60 percent completed all serial questionnaires with detailed questions about problems with food. About 500 infants were characterized as having a food-related problem, and 143 (6 percent) were classified as probable FA cases by one year of age.

2.3.2 PREVALENCE RATES FOR SPECIFIC FOODS AND ANAPHYLAXIS

- **Peanut and tree nuts allergy**

  Investigators from the United States and several other countries have published prevalence rates for allergy to peanut and tree nuts. The results are presented in Tables 2.3 and 2.4 and include sensitization rates and other clinical results. Where prevalence and sensitization were measured in the same study, prevalence is always less than sensitization.

Peanut summary

- US prevalence of peanut allergy ranges from 0.4 to 0.8 percent of the population
- Prevalence of peanut allergy in Australia, France, Germany, Israel, Sweden, and the United Kingdom varies between 0.6 and 5.9 percent.

Tree nuts summary

- US prevalence of tree nuts allergy is 0.4 percent of the population
- Prevalence of tree nut allergy in France, Germany, Israel, Sweden, and the United Kingdom varies between 0.17 and 8.5 percent.

Table 2.3: Peanut allergy prevalence studies

First author[Ref #]	Age (years)	Country	Prevalence (%)	Sensitized (%)	Oral challenge + SPT
Sicherer[23]	1–65	US	0.4 % (48/12032)	-	-
Sicherer[23]	1–65	US	0.8 % (108/13493)	-	-
Liu [24]	1–85	US	-	7.6 % (625/8203)	-
Woods [25]	20–45	Australia	-	-	0.6 %(7/1141)
Rance [26]	2–14	France	0.74 % (20/2716)	-	-
Penard-Morand [27]	9–11	France	0.3 % (21/6672)	1.1 % (70/6672)	-
Schafer [28]	25–74	Germany	2.1 % (33/1537)	11.1 % (137/1537)	-
Dalal [29]	0–2	Israel	0.6 % (6/9040)	-	0.4 % (4/9040)
Marklund [30]	13–21	Sweden	5.9 % (86/1451)	-	-
Tariq [31]	4	UK	-	1.1 % (13/1218)	0.5 % (6/1218)
Grundy [32]	3–4	UK	-	3.3 % (41/1246)	1.4 % (18/1273)
Venter [33]	3	UK	-	2.0 % (13/642)	1.2 % (11/1273)
Venter [34]	6	UK	-	2.6 % (18/700)	1.8 % (15/798)
Pereira [35]	11	UK	1.9 % (14/775)	3.7 % (26/699)	1 % (8/775)
Pereira [35]	15	UK	2.5 % (19/757)	2.6 % (17/649)	0.8 % (6/757)
Du Toit [36]	4–18	UK	UK: 1.85 % (73/3942) Israel: 0.17 % (8/4657)	-	-

Table 2.4: Tree nut allergy prevalence studies

Study	Age (years)	Country	Prevalence (%)	Sensitized	Oral challenge +SPT
Sicherer[23]	1–65	US	0.4 % (48/12032)	-	-
Sicherer[23]	1–65	US	0.4 % (54/13493)	-	-
Rance [26]	2–14	France	0.74 % (20/2716)	-	-
Schafer [28]	25–74	Germany	8.5 % (130/1537)	17.8 % (274/1537)	-
Dalal [29]	0–2	Israel	0.3 % (6/9040)	-	0.2 % (4/9040)
Marklund [30]	13–21	Sweden	5.9 % (86/1451)	-	-
Tariq [31]	4	UK	-	0.2 percent (2/1218)	0.2 %
Venter [33]	3	UK	-	-	0.5 % (6/1273)
Venter [34]	6	UK	1.3 % (13/798)	-	N/A
Pereira [35]	11	UK	1.1 % (9/775)	-	1 % (8/775)
Pereira [35]	15	UK	2.2 % (17/757)	-	0.8 % (6/757)

- Seafood allergy
  - Sicherer et al.[37] in the US used random digit dialing of a national sample to estimate lifetime prevalence rate for reported seafood allergy.
    - Rates were significantly lower for children than for adults: fish allergy, 0.2 percent versus 0.5 percent (p=0.02); crustacean shellfish allergy, 0.5 percent versus 2.5 percent (p<0.001); any seafood allergy, 0.6 percent versus 2.8 percent (p=0.001)
    - Rates were higher for women than men: crustacean shellfish allergy, 2.6 percent versus 1.5 percent (p<0.001); any fish, 0.6 percent versus 0.2 percent (p<0.001)
  - Liu et al.,[24] using National Health and Nutrition Survey (NHANES) data from 2005–2006, estimated clinical food allergy to shrimp was 0.99 percent of the population and sensitization to shrimp was 5.9 percent.

- Milk and egg allergy
  - Liu et al.,[24] using the NHANES data, estimated the prevalence of milk and egg sensitization (not allergy) in the United States.
    - 5.7 percent of the population was sensitive to milk and 3.9 percent sensitive to egg

- In a Danish cohort of 1,749 children followed from birth through age 3, children were evaluated by history, milk elimination, oral challenge, and skin tests or sIgE.[38]
  - Milk allergy was suspected in 117 children (6.7 percent) and confirmed in 39 (2.2 percent). Of those, 21 had IgE-mediated allergy and the remaining 18 were classified as non-IgE-mediated.
- In a Norwegian cohort of 3,623 children followed from birth until the age of two, parents completed questionnaires regarding adverse food reactions at 6 month intervals.[38,39]
  - The cumulative incidence of adverse food reactions was 35 percent by age 2, with milk, the single food item most commonly associated with an adverse food reaction, at 11.6 percent.
  - In the second phase of the study, those children who had persistent complaints of milk or egg allergy underwent a more detailed evaluation at the age of 2 years, including skin testing and open and double-blind oral challenges.[40–41] The prevalence of cow's milk and egg allergy or intolerance at the age of 2½ years were estimated to be 1.1 percent and 1.6 percent, respectively. Most milk reactions were not IgE mediated and only 33 percent of parental reports of adverse milk reactions were confirmed. Most egg reactions were IgE mediated and 56 percent of parental reports were confirmed.

- **Anaphylaxis:** Five US studies assessed the incidence of anaphylaxis related to food; all used administrative databases or medical record review to identify cases of anaphylaxis.[42–46]
  - These studies found wide differences (from 1/100,000 population to as high as 70/100,000 population) in the rates of hospitalization or Emergency Department visits for anaphylaxis, as assessed by ICD codes or medical record review. These variations may be due to differences in the study methods or differences in the populations (Florida, New York, Minnesota).
  - The proportion of anaphylaxis cases thought to be due to foods also varied between 13 percent and 65 percent, with the lowest percentages found in studies that used more stringent diagnostic criteria for anaphylaxis.
  - One study reported that the number of hospitalizations for anaphylaxis increased with increasing age, while another study reported total cases of anaphylaxis were almost twice as high in children as in adults.

The EP agreed that any estimate of the overall U.S. incidence of anaphylaxis is unlikely to have utility because such an estimate fails to reflect the substantial variability in patient age, geographic distribution, criteria used to diagnose anaphylaxis, and the study methods used.

- Incidence and prevalence of co-morbid conditions
  - According to a recent CDC study, children with FA are about two to four times more likely to have other related conditions such as asthma (2.3 fold), AD (2.3 fold), and respiratory allergies (3.6 fold), compared with children without FA.[47]

- Several studies report on the co-occurrence of other allergic conditions in patients with FA,[48–50] such as
  - 35 to 71 percent with evidence of AD
  - 33 to 40 percent with evidence of allergic rhinitis
  - 34 to 49 percent with evidence of asthma
- In patients with both AD and FA[51]
  - 75 percent had another atopic condition
  - 44 percent had allergic rhinitis and asthma
  - 27 percent had allergic rhinitis
  - 4 percent had asthma, without another atopic condition
- The prevalence of FA in individuals with moderate to severe AD is 30 to 40 percent and these patients have clinically significant IgE-mediated FA (as assessed by some combination of convincing symptoms, skin tests, sIgE levels, or oral food challenges)[52] or a definite history of immediate reactions to food.[53]
- A retrospective review of the records of 201 children with an ICD-9 diagnosis of asthma found 88 (44 percent) have concomitant food allergy.[54]

Thus, children with food allergy may be especially likely to develop other allergic diseases. However, the above studies should be interpreted with caution since they may be subject to selection bias.

2.4 KNOWLEDGE GAPS

Studies on the incidence, prevalence, and epidemiology of food allergy are lacking, especially in the United States. It is essential that studies using consistent and appropriate diagnostic criteria be initiated to understand the incidence, prevalence, natural history, and temporal trends of food allergy and associated conditions.

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***Supplementary document identified by the EP**

SECTION 3 NATURAL HISTORY OF FOOD ALLERGY AND ASSOCIATED DISORDERS

The Expert Panel (EP) reviewed the literature on the natural history of food allergy (FA) and summarized the available data for the most common food allergens: egg, cow's milk, peanut, tree nuts, wheat, and seafood. In addition, the EP also sought to:

- Identify changes in the manifestations of FA over time, as well as changes in coexisting allergic conditions
- Identify the risk factors for FA and severity of the allergic reaction
- Identify the frequency of unintentional exposures to the food allergen and whether this has an impact on the natural history of FA

It should be noted that published studies from the United States or Canada addressing the natural history of FA typically come from selected populations (e.g., from a single clinic or hospital) that may not be representative of the general or community-based patient population with a specific FA condition. Thus, the findings of these studies may not necessarily be extrapolated to all patients with the condition.

3.1 NATURAL HISTORY OF FOOD ALLERGY

In summary: Most children with FA will eventually tolerate cow's milk, egg, and wheat; far fewer will eventually tolerate tree nuts and peanut. The time course of FA resolution in children varies by food, and may occur as late as the teenage years. A high initial level of allergen-specific IgE (sIgE) against a food is associated with a lower rate of resolution of clinical allergy over time.

An important part of the natural history of FA is determining the likelihood and the actual time of resolution of the FA.

- In children, a drop in sIgE levels is often a marker for the onset of tolerance to the food allergens. In contrast, for some foods, the onset of allergy can occur in adult life, and the FA may persist despite a drop in sIgE levels over time.
- The resolution of atopic dermatitis (AD) over time may be temporally associated with resolution of the FA. Although AD patients with FA may not be representative of all FA patients, in the opinion of the EP, AD resolution is still a useful marker for the onset of tolerance to food allergens.
- Changes in skin tests in association with resolution of the FA are less well defined, since skin tests to a food can remain positive long after tolerance to the food has developed. Nevertheless, a reduction in the size of the skin test wheal may be a marker for the onset of tolerance to the food allergen.

Because the natural history of the FA varies by the food, the natural history of each of the most common food allergies is addressed below.

3.1.1 EGG

Earlier studies, such as one from Sweden[44] and one from Spain[45] indicated that most egg-allergic infants become tolerant to egg at a young age. An estimated 66 percent of children became tolerant by age 7 in both studies.

In a retrospective review[13] of 4,958 patient records from a university allergy practice

- 17.8 percent (881) were diagnosed with egg allergy
- Egg allergy resolution or tolerance, defined as passing an egg challenge or having an egg IgE level <2 kU/L and no symptoms in 12 months occurred in
  - 11 percent of subjects by the age of 4 years
  - 26 percent of subjects by the age of 6 years
  - 53 percent of subjects by the age of 10 years
  - 82 percent of subjects by the age of 16 years
- Risk factors for persistence of egg allergy were high initial levels of egg-specific IgE, the presence of other atopic disease, and presence of other FA.

3.1.2 COW'S MILK

- Based on an earlier study at a university referral hospital, virtually all infants who have cow's milk allergy develop this condition in the first year of life, with clinical tolerance developing in about 80 percent by their fifth birthday.[14] Approximately 35 percent developed allergy to other foods.
- A more recent U.S. study, at a different university referral hospital, indicated a lower rate of development of clinical tolerance. As assessed by passing a milk challenge, 5 percent were tolerant at age 4 and 21 percent at age 8. Patients with persistent milk allergy have higher cow's milk sIgE levels in the first 2 years of life than those who developed tolerance (median 19.0 kU/L versus 1.8 kU/L; $P < 0.001$). Additional factors predictive of the acquisition of tolerance included the absence of asthma or allergic rhinitis and never having been formula fed.[15]
- The rate of decline of sIgE levels over time predicted the development of tolerance to cow's milk in children, as confirmed by oral food challenge. This study was performed in a highly selected patient population.[16]

3.1.3 PEANUT

There are five U.S. studies, all involving selected populations from specialist clinics, of the natural history of peanut allergy,[1,2,17–20] which are summarized in Table 3.1. These studies examined the development of tolerance and rates of unintentional exposure. In summary, a small percentage of children did appear to tolerate peanut as they grew older, but these children were still at risk for unintentional exposure.

768 **Table 3.1: Summary of U.S. studies of natural history of peanut allergy in children**

Ref #	Clinical site	Criteria for Diagnosis	Sample Size	Years of Study	Population Characteristics	Natural History
1	National Jewish Medical & Research Center	• History of clinical peanut hypersensitivity and/or a positive food challenge test • Positive SPT	102 (83 contributed data to the analysis)	Mean duration of follow-up 5.9 years	• 2–4 years old at start of study • Male 69 % • Initial symptoms non-life-threatening in 73 %	• 60% had accidental exposure to peanut during follow up and the severity of the initial reaction did not predict the severity of the subsequent reactions • 0–33/year was the mean adverse reactions due to unintentional exposure • 4 children selected on the basis of a low peanut sIgE had food challenges that were negative at ages 10, 8, 6 and 4 years
20	95% from Johns Hopkins University	• History of acute reaction to peanut, and positive skin test, RAST, or challenge • In some cases positive results to RAST or skin test with no history of ingesting peanuts	223	1998–2000	• > 4 years old • Male 63% • Median age at diagnosis 1.5 years • Median age at evaluation 6.5 years	• Based on the history and a low level of peanut sIgE, 85 patients underwent either open peanut challenge or DBPCFC with 48 (57%) passing the challenge. • 8 patients selected due to low peanut-specific IgE had negative food challenges at a median age 6 years
18	88% from Johns Hopkins University	• History of acute reaction to peanut, and positive skin test, RAST, or challenge • In some cases positive results to RAST or skin test with no history of ingesting peanuts	68	1997–2003	• > 4 years • Male 59 % • Median age at diagnosis 1.1 years • Median age at evaluation 8.5 years	Tolerance to peanut developed in some children as follows: • Tolerance 69% (47/68) • Possible tolerance 26% (18/68) • Recurrence 4% (3/38)
2	Duke University pediatric clinic	• Convincing clinical history and food-specific IgE or food challenge	140	2000–2006	• Male 66 % • Median age at first visit 28 months	• Unintentional exposure to peanuts after diagnosis 39 % • Developed tolerance 3%
17	National Jewish Center for Immunology and Respiratory Medicine	• All had symptoms and a positive double blind oral good challenge	32	1973–1985	• 2–14 years old • Median age at diagnosis 7 years	• No patient developed tolerance

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770

3.1.4 TREE NUTS

In an evaluation[23] of 278 patients with a positive tree nut (TN)-specific IgE

- 36 percent (101) had a history of acute reactions to TN, 12% (12) of whom had reactions to multiple TN and 63% (73) of whom had a history of moderate-to-severe reactions.
- Double blind placebo-controlled food challenge (DBPCFC) were offered to subjects if all current sIgE levels were less than 10 kU(A)/L. Nine of 20 patients who had previously reacted to TN, including some who had prior severe reactions, passed food challenges. Thus, 9% of 101 patients with a history of prior TN reactions outgrew TN allergy.
- 74 percent (14/19) of patients who had never ingested TN, but had detectable TN-specific IgE levels, passed challenges.
- Looking at specific sIgE cutoffs in these 14 patients, 58 percent with sIgE levels of 5 kU(A)/L or less and 63 percent with sIgE levels of 2 kU(A)/L or less passed challenges. Although an ideal sIgE cutoff for challenge cannot be firmly determined on the basis of these data, the authors concluded that patients aged 4 years or older with all sIgE levels of 5 kU(A)/L or less should be considered for challenge.

3.1.5 WHEAT

In a study[24] of 103 patients with wheat allergy (IgE mediated, not celiac disease), rates of resolution were

- 29 percent by 4 years
- 56 percent by 8 years
- 65 percent by 12 years

Higher wheat sIgE levels were associated with poorer outcomes. The peak wheat IgE level recorded was a useful predictor of persistent allergy ($P < 0.001$), although many children outgrew wheat allergy with even the highest levels of wheat-specific IgE. The median age of resolution of wheat allergy was approximately 6½ years in this population. In a significant minority of patients, wheat allergy persisted into adolescence.

3.1.6 SEAFOOD

There are few studies systematically assessing the natural history of allergy to seafood, which commonly has onset in adult life. In one study,[25] sera collected sequentially during a 24-month interval from 11 individuals, each with a clinical history suggesting allergy to shrimp, and 10 control subjects were evaluated for shrimp-specific IgE. Those with suggestive histories and positive tests underwent DBPCFC to shrimp.

- Seven subjects exhibited positive challenges based on objective signs and symptoms.
- Four subjects reported the subjective symptom of oropharyngeal pruritus.

- Shrimp-specific IgE levels in all subjects were relatively constant during the 24 months of the study and not affected by shrimp challenge.

3.2 NATURAL HISTORY OF LEVELS OF SPECIFIC IgE (sIgE) TO FOODS

In summary: For many patients, sIgE to foods appears within the first two years of life. Levels may increase or decrease; a decrease is often associated with the ability to tolerate the foods.

Based on the previously discussed studies pertaining to individual foods (Section 3.1), sIgE to a food commonly appears within the first two years of life, with the levels increasing or decreasing over time depending on the food. In a study[16] of patients with allergy to cow's milk and hen's egg and who had repeated DBPCFC, sIgE levels to cow's milk and hen's egg were retrospectively determined from stored serum samples obtained at the time of the food challenges.

- 42 percent (28 of 66) egg-allergic and 48percent (16 of 33) milk-allergic patients lost their allergy over time.
- For egg, decreases in sIgE levels were significantly related to the probability of developing clinical tolerance (P=0.0014).
- For milk, there also was a significant relationship between the decrease in sIgE levels and the probability of developing the ability to tolerate to milk (P=0.0175).
- Stratification into those below versus above 4 years of age at the time of first challenge revealed that in the younger age group the rate of decrease in sIgE levels over time was more predictive of the likelihood to develop clinical tolerance.
- The median level of sIgE at diagnosis was significantly lower for the group developing tolerance to egg (P <0.001), and a similar trend was seen for milk allergy (P=0.06).

These results were used to develop a model for predicting the likelihood of developing tolerance in milk and egg allergy based on the decrease in food sIgE over time.

3.3 DIFFERENCES IN NATURAL HISTORIES OF PEDIATRIC AND ADULT FOOD ALLERGY

In summary: FA in adults can reflect persistence of pediatric food allergies, (e.g., cow's milk, peanut, and tree nuts) or *de novo* sensitization to food allergens encountered after childhood. Although there is a paucity of data from U.S. studies, FA that start in adult life tends to persist and not resolve.

The data presented below is extracted from studies of FA with mixed age groups.

- In a retrospective study[26] of 601 cases of anaphylaxis with a mean age of 37 years, there were 133 cases of food-related anaphylaxis. The causative foods in descending order of frequency were crustacean shellfish, peanuts, food additives

or spices, tree nuts, beef, almonds or peaches. It should be noted in this study that anaphylaxis (in this study, this includes non-life threatening and largely cutaneous reactions) is used as a surrogate for the incidence of FA as measured by food challenge.

- A non-U.S. study[27] compared 30 cow's milk-allergic adults to 25 milk-sensitized, but tolerant, controls. The investigators found that
  - The majority of milk-allergic patients, 67% (20/30), reported severe symptoms on milk ingestion.
  - Milk-allergy was confirmed in all 11 patients participating in a DBPCFC.
  - The dose of milk protein (0.3 to 300 mg) that elicited subjective symptoms was significantly lower than the dose that elicited objective signs of reaction (300 to 9000 mg).
  - The severity of milk allergy by history and eliciting dose was not correlated with the size of the skin prick test (SPT) wheal or the level of milk-specific sIgE.
  - Patients with allergy had larger SPT reactivity than tolerant controls for whole cow's milk, alpha-lactalbumin, and beta-lactoglobulin (P=0.002, P=0.014, P=0.004, respectively) but not for casein. In contrast, sIgE to casein was higher in patients than in controls (P=0.016). No difference was observed for sIgE to alpha-lactalbumin and beta-lactoglobulin.
- Allergy to milk, egg, wheat, and soy generally resolves, thus becoming less prevalent in adults. In contrast, allergies to peanut, tree nuts, are more likely to persist.[28] Allergy to seafood most commonly develops in adulthood, and it usually persists.[46,47]

3.4 NATURAL HISTORY OF CONDITIONS THAT CO-EXIST WITH FOOD ALLERGY

In summary: FA may coexist with asthma, AD, eosinophilic esophagitis (EoE), and exercise-induced anaphylaxis. The presence of FA can be a predictor of acute, severe asthma. Moreover, food may be a trigger for exercise-induced anaphylaxis. Elimination of food allergens in sensitized individuals can improve symptoms of some concomitant co-morbid conditions.

3.4.1 ASTHMA

Four U.S. studies[10,29–31] assessed the relationship of food allergies to asthma. In addition, two studies[8,9] dealing with fatal or near fatal anaphylaxis to foods in U.S. children reported that all or almost all patients who died also had asthma. Furthermore, as already noted in numerous studies, concomitant asthma is highly prevalent among patients diagnosed with FA. These studies also drew several additional conclusions.

- Food-allergic asthmatics were more likely than the non-food allergic asthma patients to have had a hospitalization for asthma, and had increased emergency department visits for asthma.

- Sensitized (e.g., to milk, wheat, peanut, or egg) asthmatic children had a higher rate of hospitalization than non-sensitized asthmatic children and also required more steroid use.
- The presence of self-reported FA was significantly more likely in patients admitted to the ICU compared to ambulatory care asthma patients or those admitted to the hospital, but not to the ICU.
- The presence of FA is a risk factor for asthma severity. Moreover, the presence of asthma may substantially increase the risk of death from anaphylaxis to food proteins.

3.4.2 ATOPIC DERMATITIS

In summary: AD and FA are highly associated. When a FA is outgrown, the re-introduction of the food in the diet will not result in recurrence or worsening of the AD.

As noted previously, up to 37 percent of children under 5 years of age with moderate to severe AD will have IgE-mediated FA.[5] Whether FA can exacerbate AD is still controversial in part because the signs and symptoms of food allergen exposure are so pleomorphic and because well-designed relevant food allergen avoidance trials have rarely been done in AD subjects. A systematic review of nine randomized controlled trials,[32] which assessed the effects of dietary exclusions for the treatment of established AD in unselected subjects, found little evidence to support the role for food avoidance. However, several studies[33–35] found an improvement in pruritus when egg-allergic AD subjects were placed on an egg-free diet.

In a U.S. study[36] of the natural history of FA in children with AD, 75 children with a mean age of 8 months (range 3 to18 months) were diagnosed using a DBPCFC. Patients had other atopic diseases as described above in section 2.3.2. In addition

- 60 percent were allergic to a single food
- 28 percent were allergic to two foods
- 8 percent were allergic to three foods
- 4 percent were allergic to four foods
- Milk, peanut, and egg were the most likely to produce positive food challenges

After their initial diagnosis, all children were placed on allergen-restricted diets, with a history of compliance of 90 percent. After one or two years, the patients underwent repeat food challenge tests.

- 26 percent of patients lost all evidence of symptomatic FA.
- Overall, 31 percent of the 1,221 food allergies were outgrown after one year of food avoidance.
- All patients who outgrew their reactivity to a specific food had the food reintroduced into their diets with no recurrence of symptoms and no worsening of AD at a follow-up from six months to four years.

- Patients who developed both skin and respiratory tract symptoms at the initial food challenge were much less likely to outgrow their FA than patients whose initial symptoms were limited to skin only or skin and gastrointestinal tract symptoms.

3.4.3 EOSINOPHILIC ESOPHAGITIS

In summary: Eosinophilic esophagitis (EoE) is commonly associated with sensitization to foods. The natural history of EoE is that of a chronic relapsing condition. There is insufficient data to judge the impact of food sensitization on the natural history of EoE, and vice versa. There are data to support the beneficial effect of food elimination diets on the clinical course of EoE in patients who also have FA.

Three U.S. studies[37–39] examined the natural history of EoE in children, and the results are summarized in 3.2. Briefly,

- Most children were diagnosed within the first three years of life, with symptoms including emesis, abdominal pain, heartburn, dysphagia, airway symptoms, cough, and chest.[37]
- In one study,[39] symptoms were grouped into age-related categories as "refusal to eat" in toddlers, gastroesophageal reflux or vomiting in young school-age children, and dysphasia and food impaction in older children.
- In two studies with adequate follow-up, most patients remained symptomatic and resolution was uncommon. (14 percent[37] and 2 percent[39]). However, progression of eosinophilia to other parts of the gastrointestinal tract was very different. (77 percent[37] and 0 percent[39]).

Table 3.2: U.S. Studies of the Natural History of EoE

Ref #	Clinical Site	Sample Size	Years of Study	Population Characteristics	Sensitization	Clinical EoE
38	Mayo Clinic	71	1992–2003	• Male 65% • Age at diagnosis o Mean 10.5yr o Mode 12yr	60 % of patients had food allergies, most common foods: • Milk, • Peanuts • Soy beans	• 17 of 26 patients treated with fluticasone had "complete response."
37	Cincinnati's Children's Hospital	89 (57 to data follow-up)	1997–2004	• Male 79 % • White 94% • Age at diagnosis o Mean 6yr o Mode 1yr	• 39% to egg • 39% to peanut • 34% to soy • 29% to beans • 29% to cow's milk • 29% to pea • 26% to mustard	• 14% resolved • 53% resolved with relapse • 33% persisted • 77% had mucosal eosinophilia or non eosinophilic histopathology in stomach, duodenum, and colon
39	Children's Hospital in Philadelphia	562	1996–2006	• Male 75% • White 90% • Age at diagnosis o Mean 6yr o Mode 1–3 yr	• 17% to Milk • 11% to egg • 10% to wheat • 8% to soy • 8% to corn • 5% to peanut	• 2% resolved • 6% partial resolution • 0% progression to eosinophilia in colon or stomach

Two other studies[40, 41] evaluated the effect of an elimination diet in treating EoE and found

- A decrease in the number of esophageal eosinophils per high power field in 78 percent (112/146) of patients.[40]
- A reduction in clinical symptoms in 57% (75/132) patients. Almost all patients (160/164) who underwent complete dietary elimination with an amino-acid based formula showed clinical improvement.[41]

The influence of concomitant EoE on the natural history of FA is poorly understood. As discussed above, EoE is associated with a frequent sensitization to food allergens, as evidenced by the presence of IgE by skin prick tests, or delayed reactions to food antigens by atopy patch tests. Patients who present with EoE often have either a medical history of, or ongoing, clinical FA. Food sensitization in patients with EoE is mainly against the most common food allergens. Some studies in children have shown that removal of the sensitizing foods may lead to resolution of EoE.[48] The natural history of clinical FA in patients with EoE has not been well studied, but clinical experience suggests that it is the same as in patients with clinical FA without EoE. The influence of food avoidance on the ability to tolerate food in both pediatric and adult EoE patients remains to be fully defined.

3.4.4 EXERCISE-INDUCED ANAPHYLAXIS

In summary: Exercise-induced anaphylaxis in adults is triggered by foods in about a third of patients and has a natural history marked by frequent recurrence of the episodes.

A U.S. study[42] of the natural history of exercise-induced anaphylaxis comes from a survey of 279 patients aged 18 or older identified at a single center from 1980 until 1993.

- Thirty seven percent of patients reported a food trigger, most commonly crustacean shellfish (16 percent), alcohol (11 percent), tomatoes (8 percent), cheese (8 percent), and celery (7 percent).
- All patients met criteria for exercise-induced anaphylaxis (anaphylactic symptoms, urticaria, and/or angioedema with symptoms consistent with upper respiratory obstruction) or had cardiovascular collapse during exercise.
- 75 percent of the patients were female.
- The mean age was 37 years with an onset of symptoms at age 26, and the mean duration of symptoms was 10.6 years.
- The average number of episodes per year at the time of initial presentation was 14.5, but this frequency decreased to 8.3 at the time of the survey.
- Approximately 33 percent of patients had no attacks in the 12 months prior to the survey.
- The most frequently occurring symptoms were pruritus (92 percent), urticaria (86 percent), angioedema (72 percent), flushing (70 percent), and shortness of breath (51 percent).
- About 50 percent of the patients reported seasonal rhinitis or dust allergies, 19 percent also reported having asthma, and 10 percent had eczema.

Although this study suggests a role for FA in the pathophysiology of exercise-induced anaphylaxis, the results must be interpreted cautiously since the diagnosis of FA was not based on objective testing.

3.4.5 ALLERGIC RHINITIS

IgE-mediated FA does not commonly manifest as rhinitis. Similarly, allergic rhinitis is not thought to be a risk factor for the development of FA.[43]

3.5 RISK FACTORS FOR THE DEVELOPMENT OF FOOD ALLERGY

In summary: Family history of atopy and the presence of atopic dermatitis (AD) are risk factors for the development of both sensitization and confirmed FA.

A family history of atopy is a risk factor for FA as well as all other atopic disorders, as illustrated by the following three studies:

- A fourth to a third of children seen in a referral clinic under 5 years of age with moderate to severe AD will have IgE-mediated FA as determined by both the presence of sIgE to one of the six most common food allergens (milk, egg, wheat, soy, peanut, and fish) **and** either a positive DBPCFC, positive open food challenge, or a strong history of food reaction to food product.[5]
- Eighty two percent of 138 peanut allergic patients seen in a referral clinic had AD.[2]
- AD patients who developed severe dermatitis within the first 3 months of age most commonly had sIgE to cow's milk, egg, and peanut, suggesting that this group is at risk for manifesting IgE-mediated FA[6].

These studies strongly suggest that FA and moderate to severe AD occur frequently in the same child and that early-onset severe AD is associated with risk for the sensitization to food.

The mechanism of early sensitization to foods is unclear. Recent publications[7] have suggested that peanut sensitization is independently associated with

- Intake of soy milk or soy formula
- Dermatitis over joints and skin creases (clinical features of AD)
- Household consumption of peanut
- Use of peanut-oil-containing skin preparations

3.6 RISK FACTORS FOR SEVERITY OF ALLERGIC REACTIONS

In summary: The severity of allergic reactions to foods is multi-factorial and variable.[8–12] The severity of a reaction cannot be accurately predicted by the degree of severity of past reactions (also discussed in Section 3.7). The factor most commonly identified with the most severe reactions is the co-existence of asthma.

The severity of allergic reactions to food varies on

- The amount ingested
- The food form (cooked, raw, or processed)
- The co-ingestion of other foods

The severity also may be influenced by

- The age of the patient
- The degree of sensitization at the time of ingestion
- The rapidity of absorption, based on whether
  - The food is taken on an empty stomach
  - The ingestion is associated with exercise
  - The patient has other co-morbid conditions (e.g., asthma or AD)

Most patients who have had near-fatal or fatal reactions also had

- Concomitant asthma, especially severe asthma with adrenal suppression caused by chronic glucocorticoid therapy
- Delayed administration of epinephrine
- Lack of skin symptoms
- Denial of symptoms
- Concomitant intake of alcohol (which may increase absorption of the food allergen)
- Reliance on oral antihistamines alone to treat symptoms

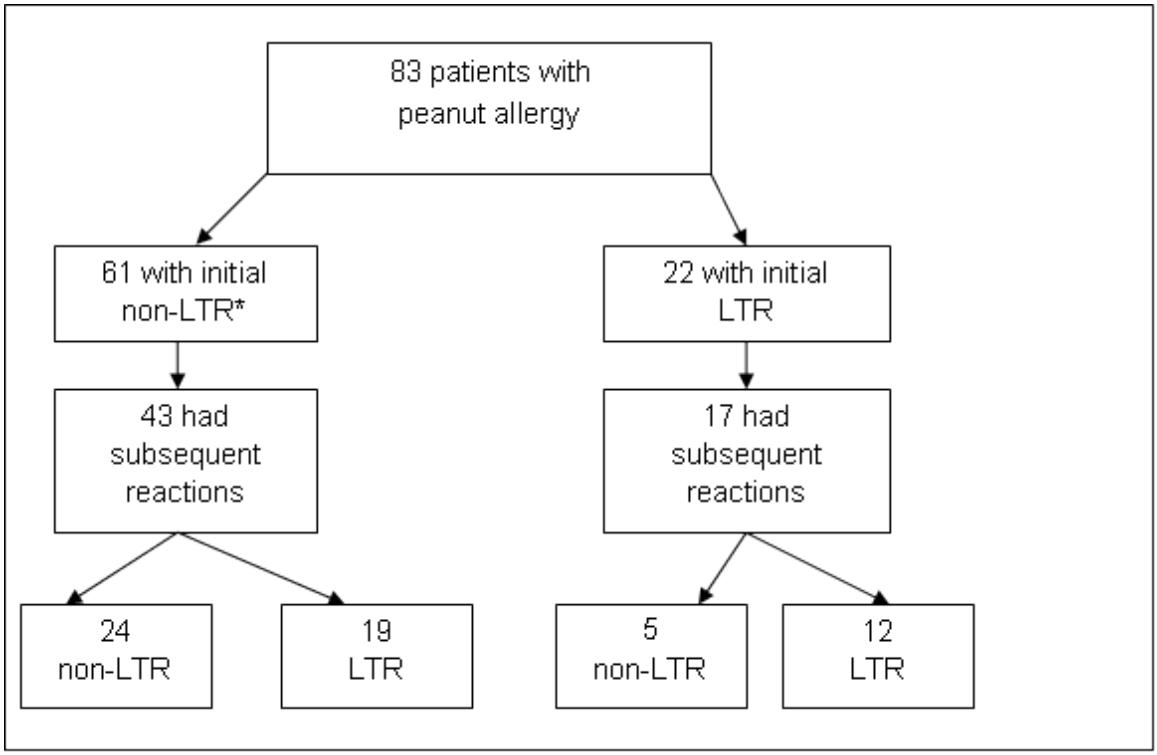
3.7 INCIDENCE, PREVALENCE AND CONSEQUENCES OF UNINTENTIONAL EXPOSURE TO FOOD ALLERGENS

In summary: Self-reported food allergic reactions frequently occur in patients with a known diagnosis of FA. Although a subset of these reactions is due to intentional exposure, most are due to unintentional exposure. Both types of exposure can be life threatening. There is no evidence that unintentional or intentional exposures to the food allergen alter the natural history of the FA.

Data on incidence/prevalence and consequences of unintentional exposures of a patient to their food allergen is derived from several longitudinal studies of individual food allergies, as follows:

- A study[1] of 83 patients with adverse reactions to peanuts prior to age 4 years, 60 percent (50/83) reported a total of 115 unintentional exposures to peanuts with adverse reactions, for a rate of 0.33 adverse reactions due to unintentional exposure per year. When the 83 patients were followed over time, the severity of the initial reaction to peanut did not predict the severity of subsequent reactions on unintentional exposures to peanut, as shown in Fig 3.1.
- Among these subsequent reactions, the rate of life-threatening reactions was high. In patients who had an initial reaction that was not life-threatening, and had a subsequent reaction, 44 percent (19/43)) had potentially life-threatening reactions during at least one of these subsequent reactions.
- In patients who had an initial reaction that was life-threatening, and had a subsequent reaction, 71 percent (12/17) had potentially life-threatening symptoms during at least one of these subsequent reactions.

Figure 3.1: The severity of the subsequent reactions to peanuts[1].



*LTR Life threatening reaction

- A retrospective chart review study[2] of pediatric patients with peanut allergy seen in a university practice between 2000 and 2006 found that unintentional ingestions occurred in 39 percent of 140 patients, with a mean of 1.8 unintentional ingestions per patient and a range of 1 to 10 ingestions. The median time to first unintentional ingestion was 12.5 months after diagnosis and 25 percent of patients reported a subsequent reaction that was more severe than the first one.
  A telephone survey[3] about unintentional exposures to peanuts in 252 children found 35 unintentional exposures occurred in 29 children over a period of 244 patient-years, yielding an annual incidence rate of 14.3 percent. Eighty five percent of the children attended schools prohibiting peanuts.
- A survey study[4] of college students with FA found that 42.2 percent (121/278) reported having had a food reaction while enrolled in a university and 27 percent (75/278) had the reaction while on campus. The reactions occurred in restaurants (21.3 percent), residence halls (19.9 percent), parent's house (18.8 percent), apartment (17.1 percent), friend's house (16.7 percent), dining hall (13.6 percent) and other (5 percent).

3.8 KNOWLEDGE GAPS

There are many gaps in the published literature on the natural history of FA. In particular, while there are several follow-up studies from single clinics, there are no data from community-based populations in the United States. Thus, the true natural history of

symptoms, co-morbid conditions, and the frequency and impact of inadvertent exposures are largely unknown.

Little is known about

- The factors that may cause higher morbidity and mortality from FA (aside from the association with asthma).
- The natural history of IgE-mediated FA in adults with the exception that crustacean shellfish allergy is thought to be more common in this age group and possibly the most common recognized food allergen.
- The differences in the range of symptoms of FA based on the age of the patient, their co-morbidities (e.g., other atopic disorders), the food allergen, its mode of preparation, or the dose of allergen.
- The differences and similarities between pediatric and adult FA
- The natural history of non-IgE but immunologic FA.

No information is available on

- The impact of treatment for ongoing asthma on the outcome of anaphylaxis

Other important areas that need to be addressed include

- The clinical and immunopathogenic impact of relevant allergen avoidance in atopic individuals with FA.
- The clinical and immunopathogenic impact of asthma on the clinical course of AD and EoE.
- The use of more aggressive management of FA (e.g., therapeutic use of anti-IgE, targeted food elimination diet, newer immunotherapeutics) to determine if it would alter the severity or magnitude of the other co-morbid conditions.

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***Supplementary document identified by the EP**

SECTION 4 DIAGNOSIS OF FOOD ALLERGY

4.1 WHEN SHOULD FOOD ALLERGY BE SUSPECTED?

Guideline 1: The Expert Panel (EP) recommends that food allergy (FA) should be considered

- In individuals presenting with anaphylaxis or any combination of symptoms listed in Table 4.1 that occur within minutes to hours of ingesting food, especially in young children and/or if symptoms have followed the ingestion of a specific food on more than one occasion
- In infants and young children diagnosed with certain disorders such as moderate to severe atopic dermatitis (AD), eosinophilic esophagitis (EoE), enterocolitis, enteropathy, and allergic proctocolitis
- In adults diagnosed with EoE

Rationale: There is sufficient evidence to support the evaluation of food allergy in patients presenting with specific allergic signs and symptoms following the ingestion of food or with certain disorders frequently associated with allergic reactions to food, even in some cases without an apparent relationship to eating.

Balance of Benefits and Harms: Identification and avoidance of foods responsible for food allergic reactions improve quality of life and potentially prevent life-threatening reactions and disorders. With the appropriate evaluation, there is a low risk of labeling someone as food allergic and adversely affecting their nutritional well-being and social interactions.

Quality of Evidence: Moderate

Contribution of Expert Opinion: Significant

Table 4.1 Symptoms of Food-allergic Reactions

Target Organ	Immediate Symptoms	Delayed Symptoms
Cutaneous	• Erythema • Pruritus • Urticaria • Morbilliform eruption • Angioedema	• Erythema • Flushing • Pruritus • Morbilliform eruption • Angioedema • Eczematous rash
Ocular	• Pruritus, • Conjunctival erythema • Tearing • Periorbital edema	• Pruritus • Conjunctival erythema • Tearing • Periorbital edema
Upper Respiratory	• Nasal congestion • Pruritus • Rhinorrhea • Sneezing	-
Lower Respiratory	• Cough • Chest tightness • Dyspnea • Wheezing • Intercostal retractions • Accessory muscle use	• Cough, dyspnea, and wheezing
Gastrointestinal (Oral)	• Angioedema of the lips, tongue, and/or palate • Oral pruritus • Tongue swelling • Swelling in the throat • Hoarseness • Dry staccato cough	-
Gastrointestinal (Lower)	• Nausea • Colicky abdominal pain • Reflux • Vomiting • Diarrhea	• Nausea • Abdominal pain • Reflux • Vomiting • Diarrhea • Hematochezia • Irritability and food refusal with weight loss (young children)
Cardiovascular	• Tachycardia (occasionally bradycardia in anaphylaxis) • Hypotension • Dizziness • Fainting • Loss of consciousness	-

When an individual presents with any combination of the symptoms listed in Table 4.1 shortly after ingesting food, a diagnosis of food allergy should be considered, especially if symptoms have followed the ingestion of a specific food on more than one occasion. Note that upper airway symptoms (e.g., nasal congestion and/or ocular pruritus) in the absence of other allergic symptoms are rarely due to a food allergy.[1]

4.1.1 TIMING OF FOOD ALLERGIC REACTIONS

Allergic reactions to food or a food additive may present with a variety of symptoms (see Table 4.1). These reactions may be

- **Immediate**, occurring within minutes to a few hours, and typically involve IgE-mediated mechanisms
- **Delayed**, occurring within several hours to a few days, and are thought to typically involve cellular mechanisms

4.1.2 IgE-MEDIATED REACTIONS TO FOOD

IgE-mediated reactions to foods are more common in young children, affecting up to 6 percent of children under 5 years of age, and are more frequently seen in children with certain atopic disorders, such as AD. For example, approximately 35 percent of children with moderate to severe AD have FA[2]. In another study, investigators found that the younger the child and the more severe the AD, the greater likelihood that the child has a FA.[7] Although any food may cause an allergic reaction, symptoms following the ingestion of certain foods should raise greater suspicion of food allergy, especially in atopic individuals. For example

- Milk, egg, and peanut account for the vast majority of allergic reactions in young children
- Peanut, tree nuts, and seafood (fish and crustacean shellfish) account for the vast majority of reactions in teenagers and adults.

Symptoms of FA should occur consistently following the ingestion of the causative food allergen, although small, sub-threshold quantities of a food allergen or extensively baked, heat-denatured foods may sometimes be ingested without inducing symptoms.

When evaluating older patients, certain complementary factors must be considered, such as exercise, alcohol consumption and use of non-steroidal anti-inflammatory drugs. Some individuals will only experience allergic reactions if they ingest specific foods in association with these factors. For example, anaphylaxis that occurs following exercise is associated with sensitization to specific foods in approximately 30 percent of cases.

Sensitization to food proteins and allergic reactions to food are much more prevalent in individuals with certain clinical disorders. For example, more than 95 percent of children and adolescents with EoE experienced marked clinical and histological improvement when placed on an allergen elimination (often elemental) diet,[74] although the causative role of IgE-mediated mechanisms in EoE is unclear.

4.1.3 MIXED IgE- AND NON-IgE-MEDIATED REACTIONS TO FOOD

Mixed IgE- and non-IgE-mediated mechanisms should be suspected when symptoms, which generally involve the gastrointestinal (GI) tract, are of a more chronic nature, do not resolve quickly, and are not closely associated with ingestion of an offending food (e.g., food protein-induced enterocolitis syndrome (FPIES) and EoE). Thus, the presence of food allergy should be suspected but the differential diagnosis will be broader as compared to IgE-mediated food allergy.

FA should be suspected when an esophageal biopsy as part of an evaluation for chronic/intermittent symptoms of gastroesophageal reflux reveals EoE, as evidenced by eosinophilia in the proximal 2/3 of the esophagus.[8] EoE can be seen at any age, but is most common in infants, children, and adolescents. In adults, symptoms of EoE include abdominal pain, dysphagia and/or food impaction. Allergic eosinophilic gastroenteritis can manifest at any age and present as chronic abdominal pain, emesis, poor appetite, failure to thrive, weight loss, anemia, or protein-losing enteropathy.

4.1.4 NON-IgE-MEDIATED REACTIONS TO FOOD

Some gastrointestinal disorders in children are frequently provoked by exposure to food proteins and thought to be caused by delayed, immune but not IgE-mediated reactions to foods, for example

- Food protein-induced enterocolitis syndrome (FPIES) (milk, soy, rice, cereal grains)[3–5]
- Food protein-induced enteropathy syndrome
- Food protein-induced allergic proctocolitis syndrome (milk, soy, egg)[6]

Adults may also develop these disorders, but they appear to be much less common than in children. Celiac disease is the exception among non-IgE-mediated reactions to food because it occurs with similar frequency in children and adults.

Two examples of non-IgE-mediated disorders are allergic proctocolitis and FPIES.[4–6,9] The former can manifest in young infants who frequently are breastfed and presents as blood-streaked or hemoccult-positive stools in an otherwise healthy appearing infant. The latter also usually occurs in young infants and manifests as chronic emesis, diarrhea, and failure to thrive. Upon re-exposure to the offending food after a period of elimination, a subacute syndrome can present with repetitive emesis and dehydration. There are also reports of adults (IgE-negative) experiencing crampy abdominal pain, severe vomiting, light-headedness, and lethargy two to three hours following the ingestion of crustacean shellfish.[73]

4.1.5 DIFFERENTIAL DIAGNOSIS OF FOOD ALLERGY

In a meta-analysis of studies evaluating FA, up to 35 percent of individuals reporting a food reaction believe they have FA,[67] whereas studies confirming FA by oral food challenge suggest a prevalence of about 3.5 percent.[68] Much of this discrepancy is due to a misclassification of adverse reactions to foods that are not allergic in origin, for

example lactose intolerance causing bloating, abdominal pain, and diarrhea after consuming milk products. There are many causes of reactions to foods that are not allergic in origin.

In the differential diagnosis of food allergies, allergic disorders from other causes, such as drugs, as well as disorders that are not immunologic in nature must be considered. The medical history is vital in excluding these alternative diagnoses, for example

- Acute allergic reactions initially attributed to a food may have been triggered by other allergens (e.g., medications, insect stings).
- In children with atopic dermatitis, eczematous flares erroneously attributed to foods are often precipitated by irritants, humidity, temperature fluctuations, and bacterial infections of the skin (e.g., *Staphylococcus aureus*).
- Chronic gastrointestinal symptoms may result from reflux, infection, anatomical disorders, metabolic abnormalities, e.g. lactose intolerance, and other causes.
- Chemical effects and irritant effects of foods may mimic allergic reactions. For example, gustatory rhinitis may occur from hot or spicy foods due to neurologic responses to temperature or capsaicin.[69]
- Tart foods may trigger an erythematous band on the skin of the cheek along the distribution of the auriculotemporal nerve in persons with gustatory flushing syndrome.[70]
- Food poisoning, due to bacterial toxins such as toxigenic *E. coli* or scombroid poisoning caused by spoiled dark-meat fish such as tuna and mahi-mahi, can mimic an allergic reaction.[71]
- For persons with eosinophilic gastrointestinal disorders, alternative diagnoses such as parasite infections, gastroesophageal reflux disease, systemic eosinophilic disorders and vasculitis should be considered.
- Behavioral and mental disorders may result in food aversion (e.g., anorexia nervosa).
- Pharmacological effects of foods, such as tryptamine (in tomatoes) and food additives may mimic some allergic symptoms of the skin and gastrointestinal tract.[72]

4.2 DIAGNOSIS OF IgE-MEDIATED FOOD ALLERGY

4.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATION

Guideline 2: Medical history and physical examination

- Medical History: The EP recommends utilizing a detailed medical history to help focus the evaluation of a food allergy. Although the medical history often provides evidence for the type of food allergic reaction and the potential causative food(s) involved, history alone cannot be considered diagnostic of food allergy.
- Physical Examination: The EP recommends performing a physical examination of the patient, which may provide signs consistent with an allergic reaction or disorder often associated with FA. However, by itself, the physical examination cannot be considered diagnostic of a FA.

Rationale: Medical history is useful for identifying food allergens that may be responsible for IgE-mediated allergic reactions, but it lacks sufficient sensitivity and specificity to definitively make a diagnosis of FA. Moreover, medical history is more useful in diagnosing "acute" food allergic reactions compared to "delayed" reactions, but usually requires further evaluation to confirm a diagnosis of FA; such as laboratory studies and/or oral food challenges.
Balance of benefits and harms: The medical history and physical examination provide evidence for suspecting FA and focus the evaluation. However, basing the diagnosis of FA on either history or physical examination alone may lead to an erroneous diagnosis of FA and may lead to unnecessarily restrictive diets that could have adverse nutritional and social consequences.
Quality of Evidence: Low
Contribution of Expert Opinion: Significant

In evaluating a patient with suspected FA, a thorough medical history is very important in identifying symptoms associated with FA (see Table 4.1) and focusing the diagnostic work-up, but alone cannot be considered diagnostic.[10,1] The nature of the reaction often suggests the underlying mechanism, either IgE-mediated (immediate) or non-IgE-mediated (delayed), and will determine the diagnostic tests to be utilized. Since none of the symptoms of FA are pathognomonic for the disorder, the medical history may be used to help identify causative allergens or to differentiate the reaction from non-allergic disorders, even though history alone does not provide sufficient sensitivity of specificity to make a diagnosis of FA.[12]

Critical questions should include the following:

- What are the symptoms of concern?
- When do they occur in relation to exposure to a given food?
- Can the food ever be eaten without these symptoms occurring?
- Have the symptoms been present at times other than after exposure to a given food?
- What treatment was given and how long did the symptoms last?

There are no findings in a physical examination that are diagnostic of food allergy. The presence of physical signs at the time of the physical examination may verify the diagnosis of an atopic disorder (e.g., urticaria, AD), or suggest prolonged symptoms (e.g., loss of body weight in patient with EoE). Physical examination may also reveal findings more suggestive of a non-allergic disorder that would require further investigation and testing.

Guideline 3: The EP recommends that parent and patient reports of food allergy must be confirmed since multiple studies demonstrate that 50 to 90 percent of presumed food allergies are not actually allergies.
Rationale: Given the low positive predictive value of self-reported symptoms, it is important that all suspected food allergy be confirmed by appropriate evaluation (e.g., food challenge, tests for allergic sensitization).

Balance of Benefits and Harm: Since unnecessary food avoidance affects quality of life and nutrition, there is possible harm in over-diagnosing FA.
Quality of Evidence: High
Contribution of expert opinion to the recommendation: Minimal

As described in Section 2.3, (see Tables 2.1 and 2.2) two systematic reviews/meta-analyses found that the prevalence of FA based on self-reported symptoms of FA was several fold higher compared to when the diagnosis was based on sensitization alone, sensitization with symptoms, or by double-blind placebo-controlled food challenge (DBPCFC).

4.2.2 METHODS TO IDENTIFY THE CAUSATIVE FOOD

When evaluating a patient for FA, the diagnostic tests selected are based upon a comprehensive medical history. The history should suggest the possible allergic mechanism involved (i.e., IgE-mediated or non-IgE-mediated), which then determines the types of testing to be pursued, and the possible foods involved. Tests selected to evaluate FA should be based on the medical history and **not** be comprised of general large panels of food allergens. In addition, diagnostic tests for non-allergic disorders may be needed depending on the differential diagnosis.

4.2.2.1 Skin Prick (Puncture) Test

Guideline 4: The EP recommends performing a skin prick test **(**SPT) to assist in the identification of foods that may be provoking IgE-mediated food allergic reactions, but the SPT alone cannot be considered diagnostic of FA.
Rationale: SPTs are safe and useful for identifying foods potentially provoking IgE-mediated food allergic reactions, but they have a low positive predictive value for the clinical diagnosis of FA.
Balance of Benefits and Harms: The reagents and methods for performing SPTs are not standardized. Nevertheless, SPTs effectively detect the presence of food-specific IgE antibodies (sIgE), but many patients have sIgE without clinical FA. Compared to oral food challenge, SPTs have low specificity and low positive predictive value for making an initial diagnosis of FA. Thus, use of SPTs in this clinical setting may lead to over-diagnosis. However, in a patient with confirmed FA, SPTs are valuable in identifying the food(s) responsible for IgE-mediated food allergy. In this clinical setting, compared to oral food challenge, SPTs have high sensitivity and high negative predictive values.
Quality of Evidence: Moderate
Contribution of Expert Opinion: Significant

SPTs provide immediate results and are the most commonly performed procedure in the evaluation of IgE-mediated FA.[13-16] However, no international standards exist for standardization of reagents for skin testing, administering, or interpreting SPTs. [13]

A positive SPT is generally considered a wheal with a mean diameter 3 mm or greater than the negative control.[14] Various studies use different methods to define a positive test, from measuring the absolute wheal size to measuring the wheal size relative to the

negative (diluent) and positive (histamine) controls. A positive SPT simply correlates with the presence of allergen-specific IgE bound to the surface of cutaneous mast cells. Although the larger the mean wheal diameter provoked, the more likely that a food allergen will be of clinical relevance, the SPT alone is not diagnostic of FA.[17–20]

When diagnosing the oral allergy syndrome, or in cases where SPTs with commercial extracts do not correlate with clinical histories, the prick technique with fresh foods, especially fruits and vegetables, may prove more sensitive.[21,22]

Negative SPTs occasionally occur in patients with IgE-mediated FA. Therefore, in cases where history is highly suggestive, further evaluation (e.g., physician-supervised oral food challenge) is necessary before telling a patient that he or she is not food allergic and may ingest the suspected food.

4.2.2.2 Intradermal Tests

Guideline 5: The EP recommends that intradermal testing should **not** be used to make a definitive diagnosis of FA.
Rationale: There is insufficient evidence to support the use of intradermal skin testing for the diagnosis of FA. Moreover, intradermal skin tests carry a higher risk of adverse reactions than SPT.
Balance of Benefits and Harms: Although intradermal testing has been suggested to be more sensitive than SPT for the diagnosis of IgE-mediated FA, there is no evidence to support such claims for protein-induced FA and insufficient evidence to support its routine use in diagnosing carbohydrate-induced food allergy. In addition, there is a greater risk of systemic adverse allergic reactions from intradermal skin tests compared to SPT.
Quality of Evidence: Low
Contribution of Expert Opinion: Significant

Intradermal testing for food allergy does not provide increased sensitivity in detecting food protein-induced allergic reactions.[14] There is suggestive but unconfirmed evidence to support its use in diagnosing a form of carbohydrate-induced IgE-mediated allergy that is a characteristic of some types of red meat allergy.[23]

4.2.2.3 Total Serum IgE

Guideline 6: The EP recommends that the routine use of measuring total serum IgE should **not** be used to make a definitive diagnosis of FA.
Rationale: There is insufficient evidence to support the proposal that measurements of total serum IgE levels can be a sensitive and specific test for FA.
Balance of Benefits and Harms: Although an elevated total serum IgE is frequently found in atopic individuals and some investigators suggest that it may be useful when interpreting allergen-specific IgE levels, the EP could find no studies to support such a claim. In addition, the sensitivity and specificity of this test compared to the outcome of oral food challenges is insufficient to warrant routine use in evaluating FA.
Quality of Evidence: Low

Contribution of Expert Opinion: Significant

Mehl et al. looked at the predictive value of the ratio of sIgE to total IgE for the diagnosis of FA compared to the DBPCFC and concluded that the ratio offered no advantage over sIgE alone in diagnosing FA.[24]

4.2.2.4 Food Allergen-Specific Serum IgE (sIgE)

Guideline 7: The EP recommends sIgE tests for identifying foods that potentially provoke IgE-mediated food allergic reactions, but alone these tests are not diagnostic of FA.
Rationale sIgE tests are useful for identifying foods potentially provoking IgE-mediated food allergic reactions, and specified "cut-off" levels may be more predictive than SPTs of clinical reactivity in certain populations, but when used alone they are not diagnostic of FA.
Balance of Benefits and Harms: sIgE tests are very useful for detecting the presence of sIgE antibodies, which indicate the presence of allergic "sensitization." Fluorescence-labeled antibody assays have been shown to have comparable sensitivity to that of SPTs, and the absolute levels of sIgE antibodies may directly correlate with likelihood of clinical reactivity when compared to oral food challenges for the identification of foods provoking IgE-mediated food allergy.
Quality of Evidence: Moderate
Contribution of Expert Opinion: Significant

Specific IgE testing and skin testing both depend on the presence of allergen-specific antibodies. Because the former test measures sIgE in the serum and the latter reflects IgE bound to cutaneous mast cells, their results may not correlate. Serum testing can be especially useful when SPTs cannot be done (e.g., extensive dermatitis or dermatographism), or when antihistamines cannot be discontinued.

Specific IgE levels were originally measured using the radioallergosorbent test (RAST), but this test has been replaced by more sensitive fluorescence enzyme-labeled assays and the term "RAST" should be abandoned.

It is important to note that results from different laboratories or different assay systems may not be comparable.[25] Wang et al. examined 50 patients who were between 2 and 20 years of age and used three different systems (Phadia ImmunoCAP, Turbo-MP, and Immulite 2000) to assess for allergy to cow's milk, hen's egg, peanut, as well as three aeroallergens.[25] Each system used slightly different forms of the antigens (e.g., skimmed cow's milk versus freeze-dried cow's milk versus whole cow's milk). Of the 50 patients, 42 had diagnosed FA. Each system provided significantly different measurements of sIgE for the same serum samples. Thus, the predictive values associated with clinical evidence of allergy for ImmunoCAP (which is a second generation in vitro assay for IgE antibody) cannot be applied to the third generation instruments, Turbo-MP and Immunolite.

The presence of sIgE reflects allergic sensitization and not necessarily clinical allergy. Several studies comparing the quantity of sIgE to oral food challenges have reported that

the greater the levels of sIgE, the higher the probability that ingestion of the food will lead to an allergic reaction. However, the predictive values varied from one study to another.[26–34]

4.2.2.5 Atopy Patch Tests (APT)

Guideline 8: The EP suggests that APT should **not** be used to make a definitive diagnosis of non-contact FA.
Rationale: There is insufficient evidence to support the use of APT for the evaluation of FA.
Balance of Benefits and Harms: While a number of studies have reported that the APT may be useful in the evaluation of FA in patients with AD and EoE, there is no agreement on the appropriate reagents, methods, or interpretation of these tests. When compared to oral food challenges, APTs show highly variable sensitivity and specificity among different studies.
Quality of Evidence: Low
Contribution of Expert Opinion: Significant

The APT is a specific type of patch test. In general, a patch test is used to determine allergic sensitivity by applying small pads soaked with allergen to the unbroken skin. The only difference between the APT and the regular patch test is the antigen that is being tested. The APT utilizes allergens (e.g., food allergens) that are typically used only for IgE-mediated reactions while the patch test utilizes antigens that are typically used for T cell-mediated reactions. The tests are both performed the same way.

The APT is an investigational tool for diagnosing FA and is generally used to assess delayed, or non-IgE-mediated, reactions to an allergen. There are no standard reagents and no studies specifically addressing the methodology of APTs, although test material is typically applied to the skin for 48 hours and read at 72 hours following application.[37,38] No studies of APT methodology met the RAND inclusion criteria, although most studies report applying foods (fresh or from powders) in aluminum discs to the skin with occlusion times of 48 hours and final reading at 72 hours after application of the food. The sensitivity and specificity of the test varies between studies and may be affected by the presence of AD and the age of the patient. No studies compared the use of different food allergen preparations. Two large studies concluded that there was no significant clinical value in using APTs for diagnosing FA.[16, 39]

4.2.2.6 Use of SPT, sIgE, and APT in Combination

Guideline 9: The EP suggests **not** using the combination of SPTs, sIgE levels, and APTs for the routine diagnosis of FA.
Rationale: There is no literature to support the proposal that the use of SPTs, allergen-specific sIgE levels, and APTs in combination for the evaluation of FA provides any significant advantage over the use of SPTs or sIgE tests alone.
Balance of Benefits and Harms: Combining the results of SPTs, sIgE levels and APTs may provide higher positive and negative predictive values than any test alone, but use of

all three tests is time consuming, inconvenient for the patient, and provides marginally improved positive and negative predictive values that may not be clinically relevant.
Quality of Evidence: Low
Contribution of Expert Opinion: Significant

A few studies show that various combinations of APT, SPT and sIgE, improved the sensitivity and specificity over the use of individual tests.[16,39,40] However, the small number of studies that calculated the proportion of patients for whom two or more tests could obviate the need for a DBPCFC found these proportions to be quite small.

4.2.2.7 Food Elimination Diets

Guideline 10: The EP suggests that elimination of one or a few specific foods from the diet may be useful in the diagnosis of FA, especially in identifying foods responsible for some non-IgE-mediated food allergic disorders, such as FPIES and proctocolitis, EoE, and Heiner's Syndrome.
Rationale: The use of an elimination diet in combination with a convincing history may be sufficient to diagnose FA in several food allergic disorders, including FPIES and proctocolitis, EoE, and Heiner's Syndrome.
Balance of Benefits and Harms: In several non-IgE-mediated food allergies, a suggestive medical history plus the elimination of the suspected food resulting in the resolution of symptoms provides compelling evidence for the diagnosis of FA. In these situations, there are no known laboratory tests that are diagnostic of the causative food, and the oral food challenge, while a potentially useful diagnostic test, may provoke significant morbidity. Thus, many physicians base the initial diagnosis on history and clearing of symptoms while on the elimination diet, and reserve the oral food challenge for evaluating the eventual "outgrowing" of the disorder.
Quality of Evidence: Low
Contribution of Expert Opinion: Significant

The EP did not find specific studies to support the diagnostic value of using dietary elimination trials or of food/symptoms diaries for the diagnosis of FA. Given the morbidity of oral food challenges in some non-IgE mediated food allergic disorders, some investigators believe that a convincing history plus clearing of symptoms with the initiation of an elimination diet is sufficient to make the diagnosis of FA. However, prolonged elimination diets consisting of multiple foods have been reported to induce severe malnutrition,[41–43] so confirmatory diagnostic studies must be performed in such cases to confirm the diagnosis of FA.

4.2.2.8 Oral Food Challenges

Guideline 11: The EP recommends using oral food challenges for diagnosing FA. The DBPCFC is the "gold standard" but the single-blind and open food challenge may be considered diagnostic in the clinical setting when the food challenge elicits no symptoms (i.e., negative challenge), or when there are objective symptoms (i.e., positive challenge) that correlate with medical history and are supported by laboratory tests.

Rationale: DBPCFC is the most specific test for diagnosing food allergy. However, due to the expense and inconvenience of DBPCFCs, single-blind and open food challenges may be used in the clinical setting if strict criteria are met.
Balance of Benefits and Harms: The DBPCFC eliminates potential bias of patients and supervising physicians that may interfere with the appropriate interpretation of food challenges, and corresponds most closely to the natural ingestion of food. Other diagnostics tests lack specificity and may lead to the unnecessary exclusion of foods from patients' diets. However, the DBPCFC is time consuming, expensive, and, like any form of oral food challenge, subjects the patient to potential severe allergic reactions. Single-blind and open food challenges are frequently used to screen patients for FA. When negative, they may be considered diagnostic in ruling out FA, and when positive (i.e. when "immediate" objective allergic symptoms are elicited), may be considered diagnostic in patients who also have a convincing medical history and supportive laboratory data.
Quality of Evidence: High
Contribution of Expert Opinion: Moderate

A positive SPT and/or sIgE test result are indicative of allergic sensitization, but these findings alone may or may not be clinically relevant. Most investigators in the field agree that verification of clinical reactivity requires well designed oral food challenge testing.[14,15,44–48]

Prior to initiating an oral food challenge, suspected foods are eliminated from the diet for two to eight weeks depending upon the type of food allergic reaction being examined.[48,49] All foods in question must be strictly avoided simultaneously. A young infant's diet can be limited to a hypoallergenic formula. For exclusively breastfed infants, either the suspected food is eliminated from the mother's diet or the baby is fed a hypoallergenic formula until the allergic food is identified.

After documenting significant improvement on dietary elimination, the challenge test is carried out while the patient is on minimal or no symptomatic medication. The test should be designed and performed under medical supervision to document the dose that provoked the reaction and to administer symptomatic treatment, which may require management of anaphylaxis (Section 6), and the medical personnel should have experience in carrying out such challenges. Food challenge begins with a low dose (intended to be lower than a dose that can induce a reaction[51,52]), which is then gradually increased, while monitoring for any symptoms, until a cumulative dose at least equal to the usually eaten quantity is reached. The challenge may be carried out in an open fashion in infants but in older children, single-blind or DBPCFCs may be necessary to minimize the bias.

Using DBPCFC, several studies have shown that only about a third of the suspected foods are found to be truly allergic. In addition to verifying FA, challenge testing prevents unnecessary dietary avoidance and enhances compliance with the elimination diet. Nevertheless, because of the risk of a severe reaction, intentional challenge should be avoided in patients who have recently experienced a life-threatening reaction to a

particular food, particularly if it occurred more than once. In the case of post-prandial exercise-induced reactions, food challenge should be followed by exercise.[50]

There is currently no internationally-accepted, standardized protocol for performing and interpreting DBPCFCs, although reviews outlining benefits and deficiencies have been published. [51–52]

4.2.2.9 Non-standardized and Unproven Procedures

Guideline 12: The EP does **not** recommend the use of any of the following non-standardized tests for the routine evaluation of food allergy

- Basophil histamine release/activation[53,54]
- Lymphocyte stimulation[55,56]
- Facial thermogaphy[57]
- Gastric juice analysis[58]
- Endoscopic allergen provocation[59–61]
- Allergen-specific IgG
- Allergen-specific IgG_4
- Cytotoxic assays
- Electrodermal test (Vega)
- Mediator Release Assay (LEAP diet)

Rationale: These non-standardized tests have not been shown to be of value in the diagnosis of food allergy.
Balance of Benefits and Harms: The utility of these tests has not been validated for the diagnosis of FA and may result in false positive or false negative diagnoses, leading to unnecessary dietary restrictions or delaying the appropriate diagnostic workup, respectively.
Quality of Evidence: Low
Contribution of Expert Opinion: Significant

4.3 DIAGNOSIS OF NON-IgE-MEDIATED IMMUNOLOGIC ADVERSE REACTIONS TO FOOD

The diagnosis of non-IgE-mediated FA can be challenging. Prior to a diagnostic workup, it may be difficult to distinguish an IgE-mediated from a non-IgE-mediated allergy based on history and physical examination alone. There are some distinct non-IgE-mediated conditions associated with FA. T cells have been shown to play a central role in celiac disease. Studies have shown that T cells may mediate the pathogenesis of some other non-IgE-mediated adverse reactions to food. Diagnostic tools available for non-IgE-mediated reactions include DBPCFC, contact dermatitis patch testing, APT, intradermal skin testing, lymphocyte activation assays, food-specific IgG testing, and endoscopic biopsy.

Specific non-IgE-mediated adverse reactions to foods include:

- Eosinophilic gastrointestinal diseases (EGIDs)
- Food protein-induced enterocolitis syndrome (FPIES)

- Allergic proctocolitis (AP)
- Contact urticaria
- Allergic contact dermatitis (ACD)
- Systemic contact dermatitis
- Heiner's syndrome

4.3.1 EOSINOPHILIC GASTROINTESTINAL DISEASES (EGIDS)

Guideline 13: The EP suggests using SPTs, sIgE tests, and APTs to help identify foods that may be responsible for EoE, but these tests alone are not sufficient to make the diagnosis of FA. The role of these tests in the diagnosis of other EGIDs has not been established.
Rationale: SPTs, sIgE, and APTs alone are insufficient to establish a causal role for FA in EoE, but they may be useful in identifying foods that should be investigated further with other diagnostic tests, such as dietary elimination, oral food challenges, and endoscopy and esophageal biopsy.
Balance of Benefits and Harms: Some studies suggest that SPTs, sIgE levels, and APTs may be of value in identifying foods that cause symptoms of EoE. However, the utility of these tests has not been validated for the diagnosis of FA in EoE or other EGIDs and may result in false positive or false negative diagnoses.
Quality of Evidence: Low
Contribution of Expert Opinion: Significant

EGIDs are a diverse group of intestinal diseases that require endoscopic analysis with mucosal biopsy to make the diagnosis. The diagnosis of EoE is defined by an esophageal biopsy with the finding of >15–20 eosinophils per high power field. The gold standard for establishing FA as the cause of EoE is resolution of symptoms and esophageal eosinophilia following dietary elimination, and recurrence of esophageal eosinophilia with reintroduction of the suspected food.[8]

Because food allergens are thought to play a large role in the pathogenesis of these diseases, sIgE tests and SPTs are used to identify potentially causative foods and design an optimal elimination diet. However, little evidence supports the use of these tests in predicting the severity of EGID symptoms,[62] and no studies have systematically assessed the positive and negative predictive values of SPT or sIgE results in evaluating the potential causal role of food allergy in EoE. Results of APT from one study suggest some benefit in their use for identifying suspect food allergens,[62] but this has not been confirmed in other studies.

4.3.2 FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME (FPIES)

Guideline 14: The EP recommends using the medical history and oral food challenge to establish a diagnosis of FPIES. However, given the potential morbidity provoked by the oral food challenge, a diagnosis may be based on a definitive history and absence of symptoms when the causative food is eliminated from the diet.

Rationale: FPIES is diagnosed based on a supportive medical history, resolution of symptoms with the elimination of the causative food, and in many cases, provocation of symptoms following an open or single-blind oral food challenge.
Balance of Benefits and Harms: There are no laboratory studies with demonstrated specificity and sensitivity to diagnose FPIES, so an oral food challenge is necessary to establish the diagnosis. Although the food challenge may induce significant symptoms, there are no alternative methods with adequate predictability to diagnose FPIES. However, when the history is very compelling (e.g., two or more reactions with classic symptoms to the same food in a six-month period and symptoms are eliminated when the causative food is removed from the diet), a food challenge may not be necessary to make the diagnosis. Since this disorder often lasts only a few years, however, subsequent oral food challenges are warranted to determine when FPIES has resolved and food allergen elimination diets can be terminated.
Quality of Evidence: High
Contribution of Expert Opinion: Moderate

FPIES is a severe systemic response to food protein that typically occurs one to four hours after the ingestion of the causative food and frequently develops in the first few years of life. Symptoms include vomiting, diarrhea, acidosis, and in some cases shock.[4,5,63]

Since FPIES occurs when the infant's diet is quite limited, history is often helpful in identifying food triggers. Because FPIES is a non-IgE-mediated disorder, sIgE tests and SPT are typically negative. Endoscopy may reveal a mixed eosinophilic and neutrophilic infiltrate but is not required to make the diagnosis. When young infants develop FPIES to one formula or food they are at greater risk of developing allergic reactions to other whole protein formulas. Therefore, hypoallergenic formulas are recommended.[4,64] Because hypotension may develop in up to 15 percent of cases, children should be challenged in a setting where intravenous hydration is readily available.[48]

4.3.3 ALLERGIC PROCTOCOLITIS (AP)

Guideline 15: The EP recommends using the clinical history, resolution of symptoms when the causative food is eliminated from the diet, and recurrence of symptoms following an oral food challenge to diagnose allergic proctocolitis.
Rationale: The evidence supports the conclusion that food protein-induced AP can be diagnosed based on a supportive medical history, resolution of symptoms with the elimination of the causative food, and provocation of symptoms following an oral food challenge.
Balance of Benefits and Harms: There are no laboratory studies with sufficient specificity and sensitivity to diagnose food protein-induced AP, so an oral food challenge is necessary to establish the diagnosis. Although the food challenge may induce blood in the stools, symptoms of AP are generally benign and there are no alternative methods with adequate predictability to diagnose allergic colitis. In cases with a classic history of AP, a normal physical examination and resolution of symptoms following elimination of the causative food leads many investigators to believe that an oral food challenge is not required to establish the diagnosis. Since this disorder often lasts only a few years,

repeated challenges are warranted to determine when food allergen elimination diets can be terminated.
Quality of Evidence: Moderate
Contribution of Expert Opinion: Significant

AP is a common transient disease of infancy that manifests itself as the passage of mucoid, blood-streaked stools in an otherwise healthy infant.[6] Typically AP is associated with the ingestion of cow's milk, soy milk, or human breast milk during infancy. Because AP is a non-IgE-mediated food allergy, sIgE and SPTs are typically negative. Although colonoscopy and biopsy are not generally necessary to make the diagnosis, the procedure will reveal lesions that are confined to the large bowel and consist of mucosal edema with infiltration of eosinophils in the epithelium and lamina propria. In severe lesions with crypt destruction, polymorphonuclear leukocytes are also prominent.[65]

4.3.4 CONTACT URTICARIA

Guideline 16: The EP suggests using the clinical history including the absence of symptoms while the causative food is avoided, positive sIgE or SPTs, and positive immediate epicutaneous skin tests to establish the diagnosis of food-induced contact urticaria.
Rationale: There are a limited number of well-controlled studies to demonstrate the utility of these methods in diagnosing contact urticaria, but traditionally they have been used and found to correlate with clinical symptoms.
Balance of Benefits and Harms: Although, there are few well-controlled studies to demonstrate the benefits of these methods in diagnosing contact urticaria, the potential harm of avoiding contact with foods provoking such symptoms appears to be minimal.
Strength of Recommendation: Moderate
Contribution of Expert Opinion: Significant

Contact urticaria can be of two types, either IgE mediated or non-IgE mediated. In IgE-mediated contact urticaria, substances present in foods interact with allergen-specific IgE bound to cutaneous mast cells, leading to the release of histamine and other inflammatory mediators. Localized or generalized urticaria, as well as systemic symptoms may result. In non-IgE-mediated adverse reactions to food, systemic symptoms are rarely seen. Immunologic contact urticaria may be assessed with patch tests, SPT or sIgE testing, although there is no standardization of diagnostic methodology.

4.3.5 ALLERGIC CONTACT DERMATITIS (ACD)

Guideline 17: The EP recommends using the clinical history, which includes the absence of symptoms while the causative food is avoided, and positive patch tests to diagnose ACD.
Rationale: There are a limited number of well-controlled studies demonstrating the utility of these methods in diagnosing ACD. However, the concept that patch testing can be useful in establishing the diagnosis of ACD is based on both the underlying

immunologic mechanism involved in the disease and observations from general medical practice.

Balance of Benefits and Harms: Traditionally patch testing has been used to support history in diagnosing ACD. While there are insufficient well-controlled studies to demonstrate the benefits of these methods in diagnosing ACD, the testing method largely reflects the immunopathogenic mechanism involved and the harm of avoiding contact with the food identified by this method appears minimal.

Quality of Evidence: Moderate

Contribution of Expert Opinion: Significant

ACD is a cell-mediated allergic reaction and may be triggered by foods or contaminants in foods. The immediate reactions in ACD may be initiated by contact with chemical moieties in the food, such as oleoresins in fruits and vegetables or spices. Examples include touching garlic causing contact dermatitis of the hands, mango causing perioral dermatitis, or raw chestnut causing hand and perianal dermatitis.[66] A detailed history will aid in the diagnosis of ACD. Patch testing may be performed with standardized contact allergens or suspected allergens (i.e., food allergens) applied to a healthy area of the skin with eczematous reactions assessed 48 to 72 hours later.[67] Positive reactions must be distinguished from simple irritant reactions. Furthermore, positive tests are a sign of sensitization to the allergen, but the clinical relevance of such sensitization needs to be assessed in the context of other clinical signs.

4.3.6 SYSTEMIC CONTACT DERMATITIS

Guideline 18: The EP suggests using the clinical history including the resolution of symptoms while the causative food is avoided, and positive patch tests to establish the diagnosis of systemic contact dermatitis.

Rationale: There are insufficient well-controlled studies to demonstrate the utility of these methods in diagnosing systemic contact dermatitis.

Balance of Benefits and Harms: Traditionally patch testing has been used to support a suggestive history in diagnosing this rare condition. Although there are insufficient well-controlled studies to demonstrate the benefits of these methods in diagnosing systemic contact dermatitis, the harm of eliminating a small number of foods on this basis appears minimal.

Quality of Evidence: Low

Contribution of Expert Opinion: Significant

Systemic contact dermatitis is a rare disorder consisting of generalized eczematous dermatitis associated with systemic symptoms such as fever, headache, rhinitis, and gastrointestinal complaints that develop after oral or parenteral allergen exposure to a food allergen, to which the individual has been sensitized through the skin. Metals and fragrances are allergens that play an important role in food-associated systemic contact dermatitis. Metals found in foods and associated with systemic contact dermatitis include nickel, cobalt, and chrome. Balsam of Peru, a fragrance associated with systemic contact dermatitis, consists of several chemicals, including cinnamic acid, cinnamaldehyde, cinnamic alcohol, vanillin, eugenol, methyl cinnamate, and benzyl cinnamate. This fragrance may be present in alcohol, chocolate, citrus fruits, pickled vegetable, spices,

and tomatoes.[66] Patch testing with standardized contact allergens or suspected allergens may assess contact allergen sensitization, but sIgE testing is usually negative. Clinical relevance of positive patch testing requires assessment of the clinical context, and may require food elimination or food challenges.

4.3.7 HEINER'S SYNDROME

Heiner's Syndrome is a rare syndrome in infants and young children characterized by chronic or recurrent lower respiratory symptoms often associated with pulmonary infiltrates, often associated with upper respiratory symptoms, gastrointestinal symptoms, failure to thrive, and iron-deficiency anemia.[66,67] Symptoms are associated with non-IgE-mediated immune responses to cow's milk with precipitating antibodies to cow's milk protein fractions, and often evidence of peripheral eosinophilia, iron deficiency, and deposits of immunoglobulins and C3 in lung biopsies in some cases. Milk elimination leads to marked improvement in symptoms within days and clearing of pulmonary infiltrates within weeks.[67] The immunopathogenesis of this disorder is not understood, but seems to combine cellular and immune-complex reactions causing alveolar vasculitis. In severe cases, alveolar bleeding leads to pulmonary hemosiderosis. There is no evidence for involvement of milk-specific IgE in this disease.

4.4 KNOWLEDGE GAPS

At the current time, oral food challenges provide the "gold standard" for diagnosing FA. These tests are accurate and sensitive, but they also present the greatest risk to the patient. Other laboratory tests used to diagnose FA, while safer for the patient, all have significant drawbacks, for example

- SPTs and measurements of allergen-specific IgE antibodies to detect sensitization to foods provide very sensitive means of identifying foods that **may be** responsible for IgE-mediated food allergic reactions. However, these tests have poor specificity and show relatively poor overall correlation with clinical reactivity. Consequently, if used alone, they lead to a gross over-diagnosis of clinical allergic reactivity.
- Assays based upon food allergen epitope specificity[75,76]or component protein-based assays[77] may prove to be more specific, but further studies are necessary to determine their efficacy.
- Sensitive and specific laboratory tests for diagnosing non-IgE-mediated food allergy are almost completely lacking.

The lack of objective data available to adequately evaluate existing tests to diagnose FA is reflected in the fact that of 18 guidelines proposed in this section, 15 are heavily dependent on expert opinion and only three are based on evidence of "high quality."

In conclusion, studies to identify sensitive and specific biomarkers that correlate with clinical reactivity to both IgE- and non-IgE-mediated food allergic reactions and clinical FA will be needed for the development of newer and safer laboratory tests.

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*** Supplementary document identified by the EP**

SECTION 5 MANAGEMENT OF NON-ACUTE ALLERGIC REACTIONS AND PREVENTION OF FOOD ALLERGY

This section of the Guidelines addresses the management and prevention of non-acute (and non-severe) allergic reactions to food in individuals diagnosed with food allergy (FA). Management of individuals at risk for developing FA and specific concerns about vaccination in patients with egg allergy are also addressed.

5.1 MANAGEMENT OF INDIVIDUALS WITH FA

5.1.1 DIETARY AVOIDANCE OF SPECIFIC ALLERGENS IN IgE-MEDIATED FA

Guideline 19: The Expert Panel recommends that patients with documented IgE-mediated FA should avoid ingesting their specific allergen or allergens.
Rationale: The EP recognizes that allergen avoidance is a strategy that is unproven in randomized controlled trials. However, allergen avoidance is currently the safest strategy for managing FA.
Balance of benefits and harm: For patients with FA, ingesting food allergens can cause allergic reactions ranging in severity from mild to life threatening. Carefully planned allergen-free diets can provide sufficient nutrients to maintain a healthy and active life. In addition, there is no evidence that strict food avoidance (compared to less strict avoidance) has any effect on the rate of natural remission to a specific food allergen.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

5.1.2 DIETARY AVOIDANCE OF SPECIFIC ALLERGENS IN NON-IgE-MEDIATED FA

Guideline 20: The EP recommends that individuals with non-IgE-mediated FA should avoid ingesting their specific allergen or allergens.
Rationale: The literature cannot readily be divided on the basis of IgE-mediated and non-IgE-mediated reactions. In general, the management of non-IgE-mediated FA is similar to IgE-mediated FA in that the clinical history, the age of the individual, and the specific food allergen are all-important considerations in developing the management plan. Although there are relatively few high-quality studies regarding treatment for non-IgE-mediated FA, the bulk of the evidence suggests that food avoidance is the best management plan.
Balance of benefits and harm: For patients with FA, ingesting trigger foods can cause reactions ranging in severity from mild to life threatening. Carefully planned allergen-free diets can provide sufficient nutrients to maintain a healthy and active life. In addition, there is no evidence that strict food avoidance (compared to less strict avoidance) has any effect on the rate of natural remission to a specific food allergen.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

5.1.3 EFFECTS OF DIETARY AVOIDANCE ON ASSOCIATED AND CO-MORBID CONDITIONS SUCH AS ATOPIC DERMATITIS (AD), ASTHMA, AND ESOPHAGEAL ESOPHAGITIS (EoE)

Guideline 21: In patients with documented or proven FA, who also have AD, asthma, or EoE, the EP recommends avoidance of the food allergen.
Rationale: There is only limited study data on this issue. In appropriately diagnosed individuals with FA, food allergen avoidance may reduce the severity of AD or EoE. Current evidence is not available to indicate whether food allergen avoidance will alter the course of asthma, AD, or EoE.
Balance of benefits and harm: This approach is not a further burden for patients already practicing food avoidance to manage FA.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

In a nonrandomized comparative study, Agata et al.[12] concluded that an elimination diet is a good treatment for AD associated with FA and that specific IgE to food antigens were useful as indices of the effect of elimination diets. However, it is important to note that the study was conducted in a small number of patients and the evidence quality is considered low.

Guideline 22: In patients without documented or proven FA, the EP does **not** recommend avoiding potentially allergenic foods as a means of managing AD, EoE, or asthma.
Rationale: There is no evidence to suggest avoiding food allergens reduces the severity of AD, EoE, or asthma in patients who are not sensitized and have not demonstrated specific clinical reactivity to foods.
Balance of benefits and harm: Unnecessary food avoidance could place patients at risk for nutritional deficiencies and growth deficits. There is no known benefit to avoiding potentially allergenic foods (e.g., egg, milk, peanut, tree nut, fish, crustacean shellfish).
Quality of evidence: Moderate
Contribution of expert opinion to the recommendation: Moderate

The EP identified two systematic, high-quality reviews that evaluated the effect of dietary exclusion for treating AD.

- The review by Kramer et al.[10] assessed whether maternal dietary antigen avoidance during lactation by mothers of infants with AD could reduce severity. One small trial (n=17) that met inclusion criteria for this part of the review found no significant reduction in eczema area score (mean difference -0.8; 95% CI -4.43 - 2.83) or eczema activity score (mean difference -1.4; 95% CI -7.18 to 4.38) between infants whose mothers avoided dietary antigens and those whose mothers followed a usual diet.
- The review by Bath-Hextall et al.[11] evaluated the effect of dietary exclusion by patients for treating established AD. Nine low-quality randomized controlled trials (RCTs) were found, of which only two were sufficiently similar to combine. Six of the RCTs examined milk and egg exclusion, one was a study of a diet

including only a few foods, and two evaluated elemental diets. The authors found no evidence to support the use of these dietary exclusion strategies for treating AD in an unselected population.

Similarly, the EP did not find any studies specifically addressing food allergen avoidance in other co-morbid conditions, such as asthma and EoE, when patients do not have documented or proven FA.

5.1.4 FOOD AVOIDANCE AND NUTRITIONAL STATUS

Guideline 23: The EP recommends nutritional counseling and regular growth monitoring for all children with FA.
Rationale: Although few studies have evaluated whether food allergen avoidance results in nutritional deficiency, the EP acknowledges that obtaining adequate nutrition is a concern in this population.
Balance of benefits and harm: Avoidance of specific allergens can limit the availability of nutritious food choices. Nutrition counseling can help patients plan and consume an allergen-free, yet nutritionally adequate diet.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

No randomized clinical studies have been undertaken to address whether food allergen avoidance diminishes nutritional status. However, studies[1,2] in which growth measurements were evaluated against diet records suggest children with FA are at risk for inadequate nutritional intake.

Christie et al.[1] estimated energy and nutrient intakes based on 3-day diet records. The age-matched, consecutive sampling, cross-sectional study had 98 children with FA and 99 without. The study found that

- Children with two or more FAs were shorter than those with one FA ($p < 0.05$), based on height-for-age percentiles.
- More children with cow's milk allergy or multiple food allergies consumed dietary calcium that was less than the age- and gender-specific recommendations compared with children without cow's milk allergy and/or one FA.
- The possibility of consuming a less-than-recommended intake of calcium and vitamin D in children with FA was less if the child received nutrition counseling ($p < 0.05$) or consumed a safe infant/toddler commercial formula or calcium-fortified soy beverage.

Tiainen et al.[2] collected 6-day food records for 18 children with cow's milk allergy and 20 healthy children, and found

- There was no difference in caloric intake between the two groups.
- Protein intake by the allergic children was lower (39 g versus 48 g; $p < 0.05$) and fat intake was higher (47 g versus 39 g; $p < 0.05$) than that of the healthy children.

- While no overt nutritional problems were found, the height-for-age was lower in the children with cow's milk allergy (-0.6 versus 0.2 SD units; $p < 0.05$) as compared with healthy children.

5.1.5 FOOD LABELING IN FA MANAGEMENT

Guideline 24: The EP suggests that patients with FA and their caregivers receive education and training on how to interpret ingredient lists on food labels and how to recognize incomplete labeling of ingredients.
Rationale: Current standards under the Food Allergen Labeling and Consumer Protection Act (FALCPA) include the use of precautionary ingredient labeling (e.g., "this product may contain trace amounts of allergen"), and such precautionary labeling is meant to communicate potential risk. Nevertheless, ingredient labeling is not completely effective in preventing unintentional exposure to allergens.
Balance of benefits and harm: Ingredient lists on food packages can help consumers identify the contents of products, but are often incomplete or difficult to interpret. No studies specifically evaluating the effectiveness of FALCPA were found. Incomplete or difficult-to-interpret ingredient labeling places patients at risk for unintentional exposure to allergens.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

FALCPA, which was passed by the U.S. Congress in 2004, identified eight major food allergens (peanut, tree nuts, egg, milk, soy, wheat, fish, and crustacean shellfish) that are responsible for 90 percent or more of serious adverse food reactions in the United States. Under FALCPA, products containing these major food allergens must clearly list the food allergen on the label in simple English. The one exemption is for protein from highly refined oils and their derivatives. Food labels containing disclaimers that the food "may contain" trace amounts of a major food allergen can leave consumers without adequate knowledge to make objective decisions.

The EP identified ten studies that examined whether standards for food labeling are effective in preventing food allergic reactions. No study explicitly attempted to infer a cause-and-effect relationship between changes in frequency of severe symptoms from unintentional exposure (e.g., peanut) as a consequence of implementing food labeling. The identified studies mostly assessed knowledge and preferences for food labeling.

Three studies, however, undertaken prior to FALCPA were particularly helpful in evaluating food labels.

- The first study involved 91 parents of children attending the pediatric allergy clinic at Mt. Sinai Medical Center in New York. The parents were asked to review 23 food product labels and name the food allergens to which their child was allergic and which were also present in the particular product.[3]
  - 7 percent of parents (4/60) correctly identified all 14 products containing milk.
  - 22 percent of parents (6/17) correctly identified all seven products containing soy.

- 54 percent of parents (44/82) correctly identified all five products containing peanut.
- Identification was much better for products containing wheat and egg.

- The second relevant study assessed 489 respondents (84 percent response rate) from attendees at a Food Allergy and Anaphylaxis Network (FAAN) Conference.[4]
  - Survey results indicated that ingredient labels were "always" or "frequently" read before purchasing a product by 99 percent of consumers doing the shopping and by 94 percent of people doing the cooking for food allergic patients.
  - Adverse reactions were attributed to misunderstanding of the food label in 16 percent of cases and to ingredients not declared on the label in 22 percent of cases.

- A third study[9] sought to determine the frequency and language used in voluntary advisory labels among commercially available products and to identify labeling ambiguities affecting consumers with allergy. Trained surveyors performed a supermarket survey of 20,241 unique manufactured food products (from an original assessment of 49,604 products) for use of advisory labels. Overall, 17 percent of the products surveyed contained advisory labels. As described in the review by Sicherer and Burks,[101] it is clear that numerous products have advisory labeling and ambiguities that present challenges to consumers with food allergy.

Similar problems in identification were reported in a study of parents of children with cow's milk allergy in Brazil,[5] and difficulties interpreting labels and general dissatisfaction with current labels were noted in studies from the United States, the United Kingdom, the Netherlands, and Greece.[6,7,8]

With global variations in culinary practices, labeling laws vary among geographic regions. In the European Union, for example, celery, mustard, sesame, lupine, and molluscan shellfish have been identified as major allergens. In Japan, buckwheat is an important allergen. The globalization of the food supply and exposure of Americans to new foods or culinary practices may lead to increases in the number of major food allergens in the United States.

5.1.6 WHEN TO REEVALUATE PATIENTS WITH FA

Guideline 25: The EP suggests follow-up testing for individuals with FA depending on the specific food to which the individual is allergic. Whether testing is done annually or at other intervals depends on the food in question, the age of the child, and the intervening clinical history.
Rationale: There is insufficient evidence to make a strong recommendation as to the timing for reevaluating individuals for FA.
Balance of benefits and harm: It is recognized that children will likely outgrow certain food allergies (i.e., milk, egg, soy, wheat) and be less likely to outgrow other food allergies (i.e., peanut, tree nuts, fish, crustacean shellfish). Results of follow-up testing

can guide decision-making regarding whether it is safe to introduce or re-introduce allergenic food into the diet.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

There is insufficient evidence for the EP to recommend a specific optimal interval for FA follow-up testing for each food. It is known is that allergy to some foods is outgrown quickly (e.g. milk, egg), while allergy to other foods are not (e.g. peanuts, tree nuts). If the patient has had a recent FA reaction, then there is little reason to re-test for several years. Annual testing is often the practice for determining whether allergy to milk, egg, wheat, and soy have been outgrown and the testing interval is extended to 2 to 3 years for allergy to peanut, tree nuts, fish, and crustacean shellfish. However, the EP noted that these testing schedules are not supported by objective evidence.

5.1.7 PHARMACOLOGICAL MANAGEMENT OF FA

5.1.7.1 IgE-Mediated Reactions

Guideline 26 There are **no** medications currently recommended by the EP to prevent IgE-mediated food allergic reactions.
Rationale: There is insufficient evidence to recommend the use of pharmacologic therapy in preventing food allergic reactions.
Balance of benefits and harm: Pharmacological agents have the potential to prevent or lessen the severity of food allergic reactions, but these agents may display significant side effects and predispose individuals to an increased risk for infection. Only limited safety and cost-effectiveness data are currently available.
Quality of evidence: Moderate
Contribution of expert opinion to the recommendation: Significant

Drug therapy has been used to manage FA in cases where allergen avoidance is extremely difficult or results in nutritional deficiencies. Drugs that alter the immune response to the allergen are commonly considered the most likely candidates for such therapy.

The EP identified five RCTs that evaluated immune-altering drugs to treat FA,[13–17] such as

- The effect of astemizole on oral allergy syndrome induced by consumption of hazelnuts in patients with positive SPT to birch pollen. The treatment group ingested astemizole (10 mg each morning for 14 days) and the control group ingested placebo for 14 days. Treatment was followed by two open oral provocations. The reduction in symptom severity from baseline to the final oral provocation was significantly greater in the astemizole versus placebo group ($p=0.004$).[13]
- The effect of cromolyn in children with AD and documented allergy to egg. All patients had AD as defined by Hanifin and Rajka,[19] had positive SPT, and were on a strict egg-avoidance diet for one year. Patients were treated for a week with

either cromolyn or placebo, and then were evaluated. A washout period of three to five weeks occurred before patients were crossed over to the other arm (cromolyn or placebo) for a week, and again evaluated. After one week of treatment with either cromolyn or placebo, there was no statistically significant difference in the symptom score for AD or in the response to a DBPCFC.[14]

- The effect of anti-IgE therapy in patients with peanut allergy. The administration of TNX-901, a humanized IgG_1 monoclonal antibody against IgE, increased the threshold of sensitivity to peanut on oral food challenge from a level equal to one peanut to almost nine peanuts.[15]

Given the heterogeneity of the pharmacologic interventions and allergic conditions evaluated, the EP concludes that there is insufficient evidence to recommend the use of pharmacologic therapy in preventing food allergies. However, promising results from early studies support further evaluation of astemizole and anti-IgE therapies in managing FA. Lastly, the use of antihistamines, as needed, remains the mainstay of managing (as opposed to preventing) non-severe food allergic reactions.

5.1.7.2 Non–IgE-Mediated Reactions

Guideline 27: There are **no** medications currently recommended by the EP to prevent non-IgE-mediated food allergic reactions.
Rationale: There is insufficient evidence to recommend consideration of pharmacologic therapy in patients with non-IgE-mediated FA reactions.
Balance of benefits and harm: The use of swallowed corticosteroids has the potential to lessen the severity or prevent future food allergic reactions, but these agents may display significant side effects and predispose individuals to an increased risk for infection. Nevertheless, swallowed corticosteroids have been shown to be beneficial in the treatment of EoE.
Quality of evidence: Moderate
Contribution of expert opinion to the recommendation: Significant

5.1.8 IMMUNOTHERAPY FOR FA MANAGEMENT

5.1.8.1 Allergen-Specific Immunotherapy

Guideline 28: The EP does **not** recommend using allergen-specific immunotherapy to treat FA in clinical practice settings.
Rationale: Allergen-specific immunotherapy improves clinical symptoms of FA while on treatment. However, it is currently difficult to draw conclusions on the safety of such an approach and whether clinical tolerance (i.e., improvement in clinical symptoms that persists even after allergen immunotherapy is discontinued) will develop with long-term treatment.
Balance of benefits and harm: Allergen-specific immunotherapy can improve clinical symptoms of FA for some patients; however, because of the risk of severe reaction, the approach has been used only in highly controlled settings.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

5.1.8.2 Immunotherapy with Cross-Reactive Allergens

Guideline 29: The EP does **not** recommend immunotherapy with cross-reactive allergens for treating FA.
Rationale: Although there is evidence to suggest that specific immunotherapy with cross-reactive allergens is beneficial in treating FA, additional safety and efficacy data is needed before such treatment can be recommended.
Balance of benefits and harm: It has been hypothesized that immunotherapy with cross-reactive antigens could benefit patients with FA, yet the safety of this approach has been evaluated in only one study to date.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

Immunotherapy alters the immune response to allergens as a means to treat FA. Immunotherapy can be accomplished by using small amounts of the allergic food (allergen-specific immunotherapy), or cross-reactive allergens (specific immunotherapy with cross-reactive allergens) to desensitize the patient.

Allergen-Specific Immunotherapy

- **Oral Immunotherapy**
  Seven RCT studies used desensitization protocols with the allergic food to induce tolerance.[20–26]
  - Staden et al.[20] assigned children with allergy to either milk or hen's egg to oral tolerance induction or an elimination diet.
    - 64 percent (16/25) achieved tolerance in the group that received oral tolerance compared with 35 percent (7/20) in the group that adhered to an elimination diet (p=0.05).
  - Morisset et al.[21] performed a randomized study to examine an oral desensitization protocol in children with IgE-mediated milk or egg allergies.
    - 11 percent (3/27) of the oral desensitized group for milk allergy reacted to a single (S)BPCFC compared to 40 percent (12/30) of the continued avoidance group, a significant improvement, (p<0.025). The size of the SPT wheal also decreased (p<0.002).
    - 31 percent (15/49) of the group desensitized for egg allergy reacted to a SBPCFC compared with 49 percent (17/35) of the continued avoidance group showing a trend toward improvement (p<0.10). The size of the SPT wheal also decreased (p<0.05).
  - Skripak et al.[22] studied milk oral immunotherapy in treating cow's milk allergy in patients aged 6 to 21 years. Once the immunotherapy dose of 15 mL of milk was reached, patients were then treated for 13 weeks. The milk dose threshold was higher in the group receiving oral immunotherapy (p=0.002). In a follow-up analysis, 15 participants who successfully completed the double-blind portion of the study were continued on measured dairy intake at home daily.[27] Initial milk doses ranged from 500 to 4,000 mg daily. After 13 to 75 weeks (median=17) of open-label dosing, 13 participants underwent food

challenge, at which time 46 percent (6) tolerated 16,000 mg with no reaction, and 54 percent (7) reacted at 3,000 mg to 16,000 mg.

- Longo et al.[23] studied 60 children 5 years or older with cow's milk allergy; half were assigned to an oral desensitization regimen and half kept on a milk-free diet. After 1 year
  - 36 percent in the immunotherapy regimen were completely milk tolerant
  - 54 percent could take limited amounts of milk (5 to 150 mL)
  - 10 percent were not able to complete the protocol because of persistent respiratory or abdominal complaints.
  - 0 percent on a milk-free diet could tolerate 5 mL of milk.
  - Patriarca et al.[24] evaluated oral desensitization protocols in patients with a wide variety of allergies, including milk, hen's egg, wheat, bean, and cod.
  - 75 percent (36/48) people assigned to the desensitization arm had a negative DBPCFC, compared with none of the control patients.

Non-randomized trials of egg and peanut oral immunotherapy also suggest the approach can be successful in desensitizing patients.

- In a study by Buchanan et al.[28] seven subjects with egg allergy completed a 24-month protocol for egg oral immunotherapy.
  - 57 percent (4/7) of the subjects passed a DBPCFC to 10 g egg at the conclusion of therapy.
  - 43 percent (3/7) had significantly increased threshold to egg.
  - As the study continued enrolling, the senior authors noted that of 21 new subjects, 2 were unable to reach the goal of 300 mg daily.[29]
- 93 percent (27/29) children who completed a peanut oral immunotherapy protocol were able to ingest 3.9 g peanut protein during subsequent food challenge.[30]

- Sublingual immunotherapy (SLIT)
  - In a study of the effect of sublingual hazelnut extract on patients with a hazelnut FA, the mean hazelnut quantity that provoked symptoms increased in the group receiving hazelnut extract but not in the placebo group ($p=0.02$).[25]

- Injection immunotherapy
  - In a study of the effect of injections of subcutaneous peanut extract on patients with peanut allergy, there was a decreased peanut sensitivity at one month ($p=0.0002$) but no effect on SPT or peanut-specific IgE as compared to patients with peanut allergy who did not receive subcutaneous injections. The study was suspended early for safety reasons before longer-term data could be evaluated.[26]

- **Safety issues of immunotherapy**

  Injections with peanut extract can result in repeated systemic reactions when administered in a "rush" protocol and are thus considered unsafe.[28] Oral and sublingual immunotherapy have been generally well tolerated and are safe in highly controlled clinical settings. However, few studies have provided extensive

safety data, and systemic reactions can occur at previously tolerated doses of allergen, especially after exercise or viral illness.[30]

A non-randomized study of peanut oral immunotherapy extensively evaluated safety data for 20 patients who completed all phases of therapy.[31] Subjects most often experienced significant allergic symptoms during the initial escalation, which occurred in a clinical setting. During the initial escalation day, upper respiratory tract (79 percent) and abdominal (68 percent) symptoms were most likely experienced. The risk of reaction with any home dose was 3.5 percent, and treatment was given with 0.7 percent of home doses. Two subjects received epinephrine after one home dose each.

Specific Immunotherapy with Cross-Reactive Allergens

The EP found four RCTs that used immunotherapy with cross-reactive allergens to treat food allergies.[32–35] A fifth study was not directed at specific food allergies but evaluated the oral allergy syndrome (OAS) in the setting of natural rubber latex allergy.[35]

- Patients with apple allergy received birch pollen extract immunotherapy. There was no statistically significant change in OAS response to an open apple food challenge after treatment with placebo, sublingual, or subcutaneous birch pollen extracts.[32]
- Patients with OAS to apple and hazelnuts were treated with subcutaneous immunotherapy with tree pollen extract. Improvement of OAS occurred in 67 percent (10/15) patients receiving subcutaneous immunotherapy and only 17 percent (2/12) control patients ($p<0.05$). [33]
- Birch pollen-sensitive patients with apple-induced OAS received injection immunotherapy with birch pollen extract. This treatment was found to reduce clinical apple sensitivity ($p<0.001$) but not apple-specific IgE.[34]
- A study of the safety and efficacy of sublingual immunotherapy with a latex extract in patients with food allergies found no significant difference in SPTs for food allergies after treatment.[35]

5.1.9 QUALITY OF LIFE ISSUES ASSOCIATED WITH FA

Guideline 30: The EP recommends that patients with FA and their caregivers be provided with age- and culturally-appropriate information on food allergen avoidance and emergency management.
Rationale: Food-allergen avoidance and the risk of severe allergic reactions can have substantial daily consequences for patients and their caregivers.
Balance of benefits and harm: Patients with FA and their caregivers (especially mothers) can experience anxiety and diminished quality of life because of the risk of anaphylaxis and the burden of selecting or preparing allergen-free foods. Concerns may change as FA patients mature. Knowledge and skills related to management of food allergies may improve patient and caregiver self-efficacy, quality of life, and allergen avoidance and management.
Quality of evidence: Low

Contribution of expert opinion to the recommendation: Significant

Effects of FA on Anxiety and Quality of Life

A survey by King et al.[36] of 46 families who had a child with peanut allergy, which asked members of the family to complete quality of life, anxiety, and perceived stress scales, found

- Mothers rated their own psychological ($p < 0.01$) and physical ($p < 0.05$) quality of life significantly worse than fathers rated theirs and also had higher scores than fathers for anxiety ($p < 0.05$) and stress ($p < 0.001$).
- Children with peanut allergy had significantly poorer physical health-related quality of life ($p < 0.05$), quality of life within school ($p < 0.01$), and general quality of life ($p < 0.05$) than their siblings did, as well as greater separation anxiety ($p < 0.05$).

Another survey by Ostblom et al.[37] compared 212 children who were 9 years old with FA to 221 children with allergic diseases and no FA. The survey found

- Children with FA exhibited significantly lower scores on the subscales physical functioning and social limitations within the Child Heath Questionnaire Parental Form 28.
- Children with food-related symptoms from the lower airways scored lower on self-esteem and family cohesion.

As children transition into adolescence and adulthood, they have increased responsibility regarding food selection. Their vigilance in avoiding allergens may depend in part upon whether or not they remember experiencing anaphylaxis.

- Food-allergic young adults aged 18 to 22 years who reported having experienced an anaphylactic reaction described their disease as more severe, reported more worry about their disease, and rated their parents as more overprotective than food allergic young adults who reported never having experienced anaphylaxis.[38]
- In contrast, 7 teenagers interviewed when they were 13 to 16 year old and who had a history of clinically diagnosed anaphylaxis, reported perceiving anaphylaxis as "no big deal."[39] However, most of the teens did not remember experiencing anaphylaxis. Interviewed parents reported anxiety about "handing over" responsibility for avoidance and emergency management to their children.

Effects of Food Allergy Management Plans for Patients with FA

Bollinger et al.[40] asked caregivers of food-allergic children to complete a questionnaire that evaluated their perception of the impact of their child's FA on family activities. Among the 87 families who completed the study

- More than 60 percent of caregivers reported that FA significantly affected meal preparation.
- 49 percent or more indicated that FA affected family social activities.

- 10 percent chose to home school their children because of FA.

5.1.10 VACCINATIONS IN PATIENTS WITH EGG ALLERGY

Several vaccines are grown in chick embryos or embryonic tissues and may contain small, but variable, amounts of egg protein. Recommendations for administering such vaccines to patients with egg allergy vary on the basis of the amount of egg protein in the vaccine and patient history of reaction.

5.1.10.1 Measles, Mumps, Rubella, Varicella

Guideline 31: The EP recommends that children with egg allergy, even those with a history of severe reactions, receive vaccines for measles, mumps, rubella (MMR), and varicella (V).
Rationale: MMR and MMRV vaccines are safe for children with egg allergy, even for those with a history of severe reactions.
Balance of benefits and harm: Vaccinations can prevent severe disease and generally, proof of MMR vaccination is required for school entry. Varicella vaccine is also required in most states. The measles component of the vaccine is produced in chicken-embryo fibroblasts, which may be of concern to parents with egg-allergic children. However, the MMR and MMVR vaccines are safe to administer to egg-allergic subjects because the egg protein content of these vaccines is very low.
Quality of evidence: Moderate
Contribution of expert opinion to the recommendation: Significant

Although the measles component of the MMR vaccine is produced in chicken-embryo fibroblast culture, the vaccine is safe for children with egg allergy, even those with a history of anaphylaxis.[97] The monovalent varicella vaccine does not contain preservatives or egg protein. Therefore, children with egg allergy may be given MMR or the quadrivalent MMRV vaccine without previous skin testing.[98] Many reactions to the MMR and other vaccines originally attributed to egg have been shown to be due to gelatin in the vaccine.[97] Ovalbumin is one of the egg proteins present in egg-based vaccines, and can be used as a surrogate marker for the relative levels of egg allergens present in a particular vaccine.

5.1.10.2 Influenza

Guideline 32: The EP recommends **against** administering either inactivated or live-attenuated influenza vaccines to children with a history of hives, angioedema, egg allergy plus allergic asthma, or systemic anaphylaxis to egg proteins, unless either (a) the vaccine contains less than 1.2 mcg/mL of ovalbumin; or (b) an evaluation, for allergy to the vaccine, is done first, if the vaccine's ovalbumin content is greater than 1.2 mcg/mL, or is unknown. For all children with asthma, the EP recommends using only inactivated influenza vaccine as the live attenuated influenza vaccine is contraindicated in these children.
Rationale: In the past, both the inactivated and live-attenuated influenza vaccines have been contraindicated in children with the following known allergic reactions to egg

proteins: hives, angioedema, allergic asthma, or systemic anaphylaxis. However, less severe or local manifestations of allergy to egg or feathers were not contraindications. More recent information indicates that, as long as the ovalbumin content is less than 1.2 mcg/mL, this vaccine can be safely given to individuals with egg allergy, even with a history of asthma or systemic anaphylaxis.
Balance of benefits and harm: Both the inactivated and live-attenuated influenza vaccines that are manufactured using embryonated hen eggs pose a risk of allergic response in patients with egg allergy. Influenza vaccination can prevent severe disease in susceptible individuals with asthma and egg allergy.
Quality of evidence: Moderate
Contribution of expert opinion to the recommendation: Significant

Because both the trivalent inactivated and live-attenuated influenza vaccines are developed using embyronated hen eggs, the American Academy of Pediatrics (AAP),[99] the Advisory Committee on Immunization Practices (ACIP),[102] and the British Medical Journal (BMJ)[103] have concluded that both vaccines are contraindicated in children with the following known allergic reactions to egg proteins: hives, angioedema, allergic asthma, or systemic anaphylaxis. However, the AAP believes that less severe or local manifestations of allergy to egg or feathers are not contraindications.[99]

The EP recommendations differ from those of the AAP, the ACIP, and the BMJ, based on recent clinical experience and discussions. Patients with egg allergy, even those with a history of severe allergic reactions including anaphylaxis, should receive the vaccine if they are considered at risk for complications from influenza. Such a group includes patients with asthma, who should receive only the inactivated vaccine because the live-attenuated vaccine is contraindicated.

Before giving a patient the influenza vaccine, healthcare providers should first determine the amount of ovalbumin in the vaccine.

- If the egg protein (ovalbumin) is less that 1.2 mcg/mL, the vaccine can be given without allergy testing.
- If the egg protein (ovalbumin) is unknown, or is equal to or greater than 1.2 mcg/mL, the patient should undergo SPT with the vaccine prior to administration.
    - If the result is negative, the vaccine may be given.
    - If the result is positive, the vaccine can be given, but in divided doses (e.g., 50µL followed by 450µL if the initial dose is tolerated, to deliver a 0.5ml dose) and under the supervision of a healthcare provider experienced in dealing with anaphylaxis.

A recent publication demonstrates the variability in ovalbumin content of vaccines and also demonstrates that the actual concentrations of ovalbumin are well within the manufacturers' labeling of ovalbumin content.[104]

5.1.10.3 Rabies and Yellow fever

Guideline 33: The EP recommends **against** administering either rabies or yellow fever vaccines to patients with a history of hives, angioedema, allergic asthma, or systemic anaphylaxis to egg proteins, unless an allergy evaluation and testing to the vaccine is done first.
Rationale: Both rabies and yellow fever vaccines may contain egg protein. There are no data available on whether there are concentrations of ovalbumin in these vaccines that are low enough to administer without allergy evaluation and testing.
Balance of benefits and harms: Both vaccines are manufactured in eggs, and therefore pose a risk of allergic reactions in egg-allergic people. FA evaluation and testing can provide insight into the potential for risk to an individual. Vaccination can prevent severe disease in susceptible individuals with egg allergy.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

Table 5.1: Vaccines That May Contain Egg Protein

Vaccine	Grown in	Recommendation summary
MMR and MMRV	Measles and mumps components in chick embryo fibroblasts	Administer in usual manner, even to patients with history of severe reaction to egg[97,98]
Influenza (inactivated)	Chick extraembryonic allantoic fluid	Egg-allergic patients, at risk for complications from influenza (e.g., patients with concomitant asthma) • For vaccines with less than 1.2 micrograms/mL ovalbumin, give the vaccine without allergy testing. • For vaccines with unknown content or with equal to or more than 1.2 micrograms/mL of ovalbumin, do SPT test with the vaccine before administration o If the SPT is negative, the vaccine may be given. o If the SPT is positive, the vaccine can be given in divided doses, by a healthcare provider experienced in dealing with anaphylaxis.
Influenza (live attenuated)	Chick extraembryonic allantoic fluid	Contraindicated for children with asthma. Otherwise, recommendation as for inactivated vaccine as above.
RabAvert	Chick embryo fibroblasts	For patients with egg allergy, test the vaccine prior to administration.
Yellow fever	Chick embryos	For patients with egg allergy, test the vaccine prior to administration.

The overall exposure of patients to other food allergens that might be present in preventive vaccines is unknown. There is some suggestion that cow's milk proteins are present in some vaccines, such as diphtheria, tetanus, and pertussis. No recommendations can be made concerning other vaccines without further studies.

5.2 MANAGEMENT OF INDIVIDUALS AT RISK FOR FA

5.2.1 NON-FOOD ALLERGEN AVOIDANCE IN AT-RISK PATIENTS

Guideline 34: The EP suggests that patients at risk for developing FA do **not** limit exposure to potential, non-food allergens (e.g., dust, pollen, or pet dander). Patients at risk for developing FA are defined as those with a biological parent or sibling with existing, or history of, allergic rhinitis, asthma, atopic dermatitis or food allergy. This definition of "at risk" is used throughout Section 5.2.
Rationale: There is insufficient evidence to suggest that non-food allergen avoidance has any effect on the natural history of FA.
Balance of benefits and harm: It has been hypothesized that exposure to non-food allergens could increase the likelihood of developing a FA in patients at risk for atopic disease, but there are insufficient data to support this hypothesis.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

It should be noted that the definition of "at risk" used above differs from the definition of "high risk" used below is Section 5.2.3.

5.2.2 DIETARY AVOIDANCE OF FOODS WITH CROSS REACTIVITIES IN AT-RISK PATIENTS

Guideline 35: The EP suggests that patients at risk for developing FA do **not** need to limit exposure to foods that may be cross-reactive.
Rationale: There is insufficient evidence to determine whether allergenic cross-reactivities of foods have clinical consequences.
Balance of benefits and harm: It has been hypothesized that exposure to possible cross-reactive foods could result in an allergic response. However, unnecessary food avoidance can result in inadequate nutrient intake and growth deficits.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

Because allergenic food proteins may share structural or sequence similarity with other allergenic substances, sensitization to a particular food or even an aeroallergen can result in responses to other foods containing homologous proteins. Such cross-reactivity can be limited to IgE sensitization, or be associated with clinical reactivity. Although several reports have described cross-reactivity among food allergens (see Table 5.2), the EP identified only one small relevant RCT. Klemola et al.[41] evaluated the incidence of adverse reactions or allergies to soy infant formulas in infants with cow's milk allergy syndrome and found low rates of adverse events in both the soy formula and the placebo formula. Overall, the EP concludes that there is insufficient evidence to recommend a routine evaluation of the patient for allergenic cross-reactivities to other foods, or to limit exposure to foods that may be cross-reactive.

Table 5.2: Food Allergen Cross-Reactivity

Food group	Major allergens	Sensitization (%)	Clinical reactivity (%)	Comments	Key Refs (#)
Avian and mammalian proteins	Milk: cow vs other	20–100	4–92	• High cross reactivity with goat, sheep and buffalo milk • Low cross reactivity with mare, donkey and camel	42–45
Avian and mammalian proteins	Milk vs beef/meat	-	10–20	• Sensitization to bovine serum albumin is predictor • 73–93% of beef allergic children reactive to cow milk	46–48
Avian and mammalian proteins	Egg: hen vs other	Common	†	• Cross reactivity varies among species, but common	49
Avian and mammalian proteins	Egg vs chicken/meat	-	22–32	• Bird-egg syndrome - sensitization to alpha-livetin	50
Shellfish	Shrimp vs other crustacea	50–100	38†	• Tropomyosins are panallergens that are also responsible for cross reactions to crustaceans in those with dust mite and cockroach allergy	51–54
Shellfish	Crustacea vs molluscs	47	14†	• Tropomyosins are panallergens that are also responsible for cross reactions to crustaceans in those with dust mite and cockroach allergy	51–54
Shellfish	Molluscs vs molluscs	-	49†	• Tropomyosins are panallergens that are also responsible for cross reactions to crustaceans in those with dust mite and cockroach allergy	51–54
Fish	Codfish vs other fish	5–100	30–75	• Gad c 1 (codfish parvalbumin) is panallergen	55–59
Tree nuts (TN)	TN vs other TN	92	12–(37)†	• Higher serum IgE correlations between cashew and pistachio and between pecan and walnut.	60–63
Tree nuts (TN)	TN vs peanut (legume)	59–86	33–34†	• Higher serum IgE correlations with almond and hazelnut	61 and 62
Legumes	Peanut vs soy (other)	19–79	3–5; (28–30)*	• Sensitization to lentils and chick peas may be associated with increased chance for multiple legume allergy	64–68
Cereals	Wheat vs other	47–88	21	• Most available data from patients with atopic dermatitis	69–70

† Percentage based on reported clinical reactions and not systematically evaluated by DBPCFC
* Represents DBPCFC data for lupine challenge in peanut-sensitized patients

Safety was reported for only one of four studies that examined specific immunotherapy with cross-reactive allergens.[35] In this study, no local signs or gastrointestinal symptoms were reported.

5.2.3 TESTING OF ALLERGENIC FOODS IN PATIENTS AT HIGH RISK PRIOR TO INTRODUCTION

In Summary: The EP concludes that there is insufficient evidence to recommend routine FA testing prior to the introduction of highly allergenic foods (e.g., milk, egg, and peanut) in children who are at high risk of reaction to introduction of such foods. The definition of children at high risk, in this specific situation, is of children with pre-existing severe allergic disease and/or a family history of FA. Nevertheless, there may be some value in FA evaluations that include a food challenge for a select group of patients with certain risk factors, such as having a sibling with peanut allergy[100] or evidence of another underlying FA (e.g., testing for tree nut allergy in a child with peanut allergy). It is possible that a FA evaluation prior to introduction of a food could potentially prevent allergic reactions. However, there is concern that widespread skin testing and sIgE testing is not needed and would lead to many false positive results as well as unnecessary dietary restrictions, especially if unconfirmed by oral food challenges. Overall, the risk/benefit of FA evaluation should be considered on an individual basis, especially for major food allergens (e.g., milk, egg, and peanut) in high-risk young children.

Guideline 36: For the general population, with no high-risk factors of reaction to introduction of highly allergenic foods, the EP suggests that children **not** be tested for FA to highly allergenic foods prior to their introduction into the diet. These individuals in the general population are children who do not have pre-existing severe allergic disease and also do not have a family history of FA.
Rationale: There is insufficient evidence to suggest whether, or which, foods should be tested prior to introduction.
Balance of benefits and harm: Testing prior to introduction could potentially prevent allergic reactions, but there is currently no practical consensus on which (if any) foods should be tested.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

5.2.4 TESTING IN INFANTS AND CHILDREN WITH PERSISTENT AD

Guideline 37: The EP suggests that children less than 5 years of age with moderate to severe AD be considered for FA evaluation for milk, egg, peanut, wheat, and soy, if **at least one** of the following conditions is met:

- The child has persistent AD in spite of optimized management and topical therapy.
- The child has a reliable history of an immediate reaction after ingestion of a specific food.

Rationale: There is insufficient evidence to determine the appropriate age to test for response to foods known to commonly cause IgE-mediated FA in infants or young children with AD, or other risk factors. In spite of the lack of evidence, the opinion of the EP is that if a child is less than 5 years of age and has persistent AD there is benefit to finding out if the child is allergic to a food.

Balance of benefits and harm: Early diagnosis can lead to better management of FA and reduce the risk of exposure to food antigens. However, testing is time-consuming and costly for patients and their families. Additionally, severely restrictive diets may be harmful.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

The question of when to evaluate a child, who is less than 5 years of age with moderate to severe AD, for FA has been somewhat controversial in the past 20 years. The EP identified the group of children thought to be most at risk for having FA and described them in Guideline 34 above. It should be noted that milk, egg, and peanut are most often found to be allergenic in this population. Many of these children also have sIgE to wheat and soy. Care should be taken to ensure these children are clinically allergic to a food prior to removing it completely from their diet.

The question of what to recommend for children with delayed food reactions was also considered by the EP. While a history of a possible delayed reaction to a food is clinically important, it is not diagnostic of FA, and a proper evaluation (clinical history and diagnostic testing) should be completed.

5.3 PREVENTION OF FOOD ALLERGY

5.3.1 MATERNAL DIET DURING PREGNANCY AND LACTATION

Guideline 38 The EP does **not** recommend restricting maternal diet during pregnancy or lactation as a strategy for preventing the development or clinical course of FA.
Rationale: There is insufficient evidence that maternal diet during pregnancy or lactation affects the development or clinical course of FA.
Balance of benefits and harms: Restricting exposure to food antigens either during pregnancy or through breast milk has been hypothesized as a means of preventing the development of FA, but it has not been shown conclusively to prevent FA. Adequate nutritional status during pregnancy and lactation is essential for optimal infant health, growth, and development.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

Several authors have observed that maternal dietary antigens can pass into breast milk and have hypothesized a protective effect of a diet in which certain common allergens are reduced or avoided during pregnancy and lactation by women at risk of having infants likely to go on to develop atopic disease. However, the results of several studies are conflicting.

- Kramer et al.[10] conducted a systematic review that evaluated the effect of maternal dietary avoidance on either treating or preventing atopic disease in children. The authors found no significant difference in the incidence of AD (relative risk (RR) 1.01; 95% confidence interval (CI) 0.57-1.79), asthma (RR 2.22; 95% CI 0.39-12.67), positive skin prick tests to egg (RR 0.95; 95% CI 0.52-

1.74) or milk (RR 0.86; 95% CI 0.16-4.59) during the first 18 months of life in infants whose mothers avoided dietary antigens during pregnancy. Avoidance of dietary antigens had no significant effect on the incidence of AD (RR 0.73; 95% CI 0.32-1.64).

- A non-randomized comparative study evaluated the effect of restricting maternal diet during lactation for the first 3 months after birth on the incidence of FA. Hattevig et al.[71] reported study results at 18 months and Sigurs et al.[72] reported results at 4 years of age. The authors found significantly reduced cumulative incidence and prevalence of AD at four years in children in the intervention group compared to the control group. This study was rated as low quality; however, the authors report that the two groups were comparable and matched through recruitment.

5.3.2 BREASTFEEDING

Guideline 39: The EP recommends that all infants be exclusively breastfed until 4 to 6 months of age unless breastfeeding is contraindicated for medical reasons.
Rationale: There is not strong evidence that breastfeeding has a protective role in preventing atopic disease. However, because of other benefits of breastfeeding, it is recommended that all infants, including those with a family history of atopic disease, be exclusively breastfed until 4 to 6 months of age, unless breastfeeding is contraindicated for medical reasons.
Balance of benefits and harms: Whether exclusive breastfeeding has a beneficial role in preventing atopic disease is unclear.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

The protective role of breastfeeding in preventing atopic disease is uncertain, with some studies reporting favorable outcomes associated with breastfeeding[73,74] and others reporting no effects.[75,76] The effectiveness of combining exclusive breastfeeding with other interventions to prevent atopic disease is also unclear.

In the German Nutritional Intervention Study (GINI), participants were randomly assigned to either exclusive breastfeeding or partial or complete cow's milk formula. The incidence of AD was compared.

- In a subgroup analysis, Schoetzau et al.[77] found a significantly lower risk of AD at one year of age in infants who were exclusively breastfed compared with infants who were not (9.5 percent versus 14.8 percent, respectively, p=0.015).
- Filipiak et al.[78] compared breastfeeding, use of hydrolyzed formulas, and delayed introduction of solid foods in intervention group infants with a separate control group of infants whose mothers did not receive these recommendations. They concluded that there was no evidence to support a protective effect of delayed introduction of solids for AD.

The quality of evidence for whether breastfeeding reduces the likelihood of AD is low given that the EP found only one fair quality non-randomized comparative study addressing this question and conflicting evidence from that study.

5.3.3 SPECIAL DIETS IN INFANTS AND YOUNG CHILDREN

5.3.3.1 Soy Infant Formula versus Cow's Milk Infant Formula

Guideline 40: The EP does **not** recommend using soy infant formula instead of cow's milk infant formula as a strategy for preventing the development of FA or modifying its clinical course in at-risk infants (as defined in Guidelines 34).
Rationale: The literature reports little difference between soy infant formula and cow's milk infant formula for the prevention of FA in at-risk infants.
Balance of benefits and harms: There appears to be neither long-term harm nor significant benefit in using soy infant formula.
Quality of evidence: Moderate
Contribution of expert opinion to the recommendation: Minimal

5.3.3.2 Hydrolyzed Infant Formulas versus Cow's Milk Infant Formula

Guideline 41: The EP suggests that exclusive use of extensively or partially hydrolyzed infant formulas be considered for infants who are not exclusively breastfed and are at risk for developing atopic disease. Cost or availability of extensively hydrolyzed infant formulas may be weighed as prohibitive factors.
Rationale: The evidence indicates that extensively and partially hydrolyzed infant formulas reduce the development of FA in infants at risk for developing allergic disease.
Balance of benefits and harms: There is some evidence that hydrolyzed infant formulas (particularly extensively and partially hydrolyzed infant formulas) may reduce infant and childhood allergy and cow's milk allergy in at-risk infants when compared with cow's milk infant formula. However, the cost of extensively hydrolyzed infant formulas is limiting to their practical use. There is no evidence to suggest exclusive feeding with a hydrolyzed formula is more likely to prevent atopic disease than exclusive breastfeeding.
Quality of evidence: Moderate
Contribution of expert opinion to the recommendation: Minimal

5.3.3.3 Soy Infant Formulas versus Hydrolyzed Infant Formulas versus Cow's Milk Infant Formulas

Osborn and Sinn[79] conducted a review to determine the effect of feeding adapted soy infant formula compared to human milk, hydrolyzed protein infant formulas, or cow's milk infant formula on infants who did not have a clinical FA in the first six months of life. They found three studies that compared soy infant formula to cow's milk infant formula. They reported no significant differences in incidence of childhood allergies, infant or childhood asthma, infant or childhood AD, or infant or childhood rhinitis.

5.3.3.4 Hydrolyzed Infant Formulas versus Cow's Milk Infant Formula or Breastfeeding

- Osborn and Sinn also conducted a Cochrane review comparing the effect of hydrolyzed infant formulas to cow's milk infant formula or human milk in preventing FA.[80]
  - Among four trials comparing short-term hydrolyzed infant formula feeding to human milk or cow's milk infant formula, there were no significant differences in infant or childhood cow's milk allergy.
  - In a meta-analysis of seven studies comparing prolonged feeding with hydrolyzed infant formula or cow's milk infant formula in infants at risk, the hydrolyzed infant formula resulted in a significant decrease in infant allergies (RR 0.79; 95 percent CI 0.66-0.94), but no difference in the incidence of childhood allergy (two studies, RR: 0.85, 95 percent CI 0.68-1.04). There were no significant differences in infant or childhood AD or infant or childhood asthma, rhinitis, and FA. The review provides limited evidence that prolonged feeding with hydrolyzed infant formulas in at-risk infants may reduce infant allergy and infant cow's milk allergy when compared with cow's milk infant formula.

- The review by Hays and Wood[81] included controlled trials to assess the effect of hydrolyzed infant formulas in preventing allergies when compared with breastfeeding, cow's milk infant formula, or soy infant formula, and the difference between extensively (eHF) and partially (pHF) hydrolyzed infant formulas. The authors included nine trials on eHFs (all were casein hydrolysate formulas) and 11 studies on pHFs (10 whey formulas and one casein formula). They concluded that, for both eHFs and pHFs, "the data support a protective effect…but the research falls short of meeting the American Academy of Pediatrics criteria[82] for evidence of allergy prevention."
- In the GINI study,[83,84] 2,252 infants less than 2 weeks old with a parent or sibling with a history of atopy were randomly assigned to receive one of three hydrolyzed infant formulas or cow's milk infant formula. Children were followed to 6 years. Children fed with partially hydrolyzed whey formula (pHF-W) and extensively hydrolyzed casein formula (eHF-C) were less likely to have "any allergy diagnosis from a physician" compared with children fed cow's milk infant formula (47.1%, 46.1%, versus 56% respectively). However, there was no difference between extensively hydrolyzed whey infant formula (eHF-W) and cow's milk infant formula.

Lastly, the EP found no information in the literature on the effects of specialized diets on overall growth and development.

Table 5.3 provides a summary of five randomized controlled trials that evaluated specialized infant formulas.

Table 5.3: RCTs of Specialized Formulas for Infants and Young Children

Ref #	Study Quality	Experimental Intervention Description	Control	Timing Info	Experimental Sample Size	Control Sample Size	Results
83 84	Good	Received one of the formulas: • pHF-W • eHF-W • eHF-C	Cow's milk infant formula	6 years	• 557 pHF-W • 559 eHF-W • 580 eHF-C	556	At 3 years of follow-up, there was no statistically significant effect on the incidence of asthma.
85	Fair	Lactating mothers and infants on elimination diets for cow's milk, egg, and fish, then assigned to either: • eHF-W • CMF*	Continued breast milk for >9 months. Lactating mothers and infants were on elimination diets for cow's milk, egg, and fish	18 months	• 32 eHF-W • 39 CMF	20	No statistical difference in the presence of atopic disease as judged by positive SPT or serum IgE
86	Good	Preterm infants were assigned either eHF, pHF or BMF** (with extensively hydrolyzed mixture) for 4–5 months	Infants received a standard infant formula for 4–5 months	Evaluated 4–5 months after interventio n and again at 12 months	• 20 eHF • 22 pHF • 32 BMF	26	No difference in the incidence of allergic diseases in preterm infants.
87	Fair	Formula made from chicken meat	Soy infant formula	14 days	20	18	12/18 children were intolerant to given soy formula compared with 4/ 20 children who received the chicken-meat based formula (p=0.009)
88	Good	Hypoallergenic formula supplemented with a mixture of short and long chain oligosaccharides	Hypoallergenic infant formula without the added supplement	2 years	66	68	The cumulative incidences of atopic dermatitis, recurrent wheezing, and allergic urticaria were lower in the treatment group than the control group (13.6 vs 27.9%, 7.6 vs 20.6%, 1.5 vs 10.3% respectively, p<0.05).

* CMF cow's milk formula
** BMF fortified breast milk

5.3.4 TIMING OF INTRODUCTION OF ALLERGENIC FOODS TO INFANTS

Guideline 42: The EP suggests that the introduction of solid foods should **not** be delayed beyond 4 to 6 months of age. Potentially allergenic foods may be introduced at this time as well.

Rationale: There is insufficient evidence for delaying introduction of solid foods, including potentially allergenic foods, beyond 4 to 6 months of age, even in infants at risk of developing allergic disease.

Balance of benefits and harms: Restricting exposure to food antigens during infancy has been hypothesized as a means of preventing development of FA. However, restricting

developmentally appropriate solid food variety beyond age 6 months can lead to inadequate nutrient intake, growth deficits, and feeding problems.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

Several guidelines by other organizations recommend delaying the introduction of solid foods to infants for 4 or 6 months after birth in an effort to prevent atopic disease.[89–93] However, there is no clear consensus regarding the risks and benefits of delaying the introduction of solid foods in infants beyond four to 6 months after birth.

The EP identified two studies that evaluated the effect of breastfeeding in combination with delayed introduction of solid foods in infants at risk for all allergies.

- Halmerbauer et al.[94] conducted a randomized controlled trial on environmental procedures to reduce house dust-mites as well as an educational intervention to delay introduction of solid foods. They found a significantly reduced risk of parent-reported food intolerance (vomiting, prolonged crying, diarrhea, and swollen lips after eating) in the intervention group. However, the study findings should be interpreted with caution because the study was only of fair quality and the intervention included both breastfeeding and education on delayed introduction of solid foods.
- Kajosaari[95] reported results from a comparative study that evaluated the effect of exclusive breastfeeding and delayed introduction of solid foods until 6 months in at-risk infants. They found a possible protective effect of exclusive breastfeeding for 6 months. This study was rated as poor quality because it was not randomized, and no information was provided on the comparability of the two groups.

In a comparative study of more than 900 families by Venter et al.,[96] introduction of solid foods after weaning or after 16 weeks increased the likelihood of FA at 1 and 3 years ($p=0.02$ for both ages).

The quality of evidence for this key question is low given that only two controlled trials of relatively low quality address this question. No controlled studies have addressed delayed introduction of solid foods in children who are not at risk for atopic disease.

5.4 KNOWLEDGE GAPS

With the lack of large numbers of well-controlled studies in managing and preventing FA, there are several areas where expert opinion was important in making either recommendations or suggestions. These areas include

- Food avoidance and the rate of remission of a specific FA
- The possibility of avoiding potentially allergenic foods as a means of managing AD, EoE, or asthma in patients without documented or proven FA
- Determining the timing of follow-up testing for individuals with FA on the basis of the specific allergenic food

- The use of allergen-specific immunotherapy as primary treatment for FA in clinical practice settings
- The practice of restricting maternal diet during pregnancy or lactation as a strategy to prevent the development or clinical course of FA
- The exclusive use of extensively or partially hydrolyzed infant formulas in infants who are not exclusively breastfed and are at risk for developing atopic disease.

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SECTION 6 DIAGNOSIS AND MANAGEMENT OF FOOD-INDUCED ANAPHYLAXIS AND OTHER ACUTE ALLERGIC REACTIONS TO FOODS

Food-induced anaphylaxis is a potentially fatal disorder and, like other forms of anaphylaxis, is increasing in incidence in industrialized countries.[1–6] Although food-induced anaphylaxis is not always easily recognized, the early recognition of certain signs and symptoms associated with a reaction, the timing of the reaction, and the existence of concomitant factors and disease processes help make the diagnosis. Prompt recognition and management is essential to ensure a good outcome.[7] Anaphylaxis is significantly under-recognized and under-treated,[1,2,4,8] possibly due in part to failure to appreciate anaphylaxis presenting without obvious cutaneous symptoms (10 to 20 percent of cases) or overt shock. This section of the Guidelines focuses on the diagnosis and management of food-induced anaphylaxis mediated through immune mechanisms associated with IgE antibody.

RAND Corporation conducted a systematic literature review of the topic area of food-induced anaphylaxis and found a paucity of studies meeting standards for inclusion in these Guidelines. Thus, the evidence base for the recognition, diagnosis, and especially the management of food-induced anaphylaxis, is significantly limited. Consequently, much of this section's information and cited literature are provided by the Expert Panel (EP) based on individual citations deemed to be relevant and their own experience and opinion. Much of this information is gleaned from the available literature related to anaphylaxis in general and applied specifically to food allergy.

6.1 DIAGNOSIS OF ACUTE, LIFE-THREATENING, IgE-MEDIATED FOOD ALLERGIC REACTIONS

Guideline 43: The EP recommends that the clinician considering a diagnosis of food-induced anaphylaxis should understand

- The signs and symptoms characteristic of anaphylaxis
- The timing of symptoms in association with food ingestion/exposure
- Co-morbid conditions, such as asthma, which may affect treatment and outcome
- Laboratory parameters are of limited utility in the acute care setting

Rationale: The evidence and expert opinion support prompt recognition and diagnosis of food-induced anaphylaxis.

Balance of benefits and harms: Prompt recognition and diagnosis of food-induced anaphylaxis is essential and necessary to ensure appropriate health outcomes and to prevent progression to life-threatening reactions. Potential harm, including the possibility of death, exists if the diagnosis is delayed or not recognized.

Quality of evidence: Low

Contribution of expert opinion to the recommendation: Significant

6.1.1 DEFINITION OF ANAPHYLAXIS

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death.[2,9] Typically IgE-mediated food-induced anaphylaxis is believed to involve systemic mediator release from sensitized mast cells and basophils.[10] The term "anaphylactoid" has been used in the past to indicate adverse reactions that are not IgE-mediated and typically are not life threatening. This term is imprecise and will not be used here.

6.1.2 DIAGNOSIS OF ANAPHYLAXIS

The diagnosis of anaphylaxis, either in general or specifically food-induced, is based on clinical findings and a detailed description of the acute episode, in association with known or suspected food exposure. The contribution of laboratory testing for the diagnosis of anaphylaxis is minimal, except where it may be important to diagnose the condition of food allergy. The most common food triggers for anaphylaxis are peanut, tree nuts, milk, egg, fish, and crustacean shellfish. The incidence is variable depending on age, regional diets, food preparation, amount of exposure, and timing of first exposure.[11,12] Association with a specific food is reported in up to 80 percent of anaphylaxis cases when reviewed from administrative databases or acute care settings.[3,13–21]

The medical history is an essential aspect in establishing a diagnosis of food-induced anaphylaxis. A history of prior food allergic reactions or prior diagnosis of food allergy (as defined in Section 4) in association with known ingestion of a food protein is beneficial. However, anaphylaxis in association with first-time food ingestion can occur at any age and is more common in young children. Studies have shown that anaphylaxis in the school setting occurs in as many as 20 percent of children with first-time food exposure.[22]

6.1.2.1 Diagnostic criteria for anaphylaxis

New diagnostic criteria for anaphylaxis were published in 2006[7] with the intent to help clinicians both recognize the spectrum of signs and symptoms that comprise anaphylaxis and establish a more systematic approach to its diagnosis and management. The following three criteria were established, and the presence of **any one** of these criteria indicates that anaphylaxis is highly likely:

- Acute onset of an illness (over minutes to several hours) involving skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence)
- Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

- Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)
- Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

- Reduced BP after exposure to a known allergen for that patient (minutes to several hours). Reduced BP is defined
  - In adults, as a systolic BP of less than 90 mm Hg or greater than 30 percent decrease from that person's baseline
  - In infants and children, as a low systolic BP (age-specific) or greater than 30 percent decrease in systolic BP. Low systolic BP is defined as
    - Less than 70 mm Hg for 1 month to 1 year of age
    - Less than (70 mm Hg plus twice the age) for 1 to 10 years
    - Less than 90 mm Hg for 11 to 17 years of age

  Note: In infants and young children, hypotension may be a late manifestation of hypovolemic shock. Tachycardia, in the absence of hypotension, may also indicate shock.[23]

6.1.3 SIGNS AND SYMPTOMS OF FOOD-INDUCED ANAPHYLAXIS

Usually, anaphylaxis involves more than one organ system, which helps to distinguish it from other acute reactions such as asthma exacerbations, respiratory symptoms, urticaria/angioedema, or gastrointestinal symptoms. The signs and symptoms for anaphylaxis in general are the same for food-induced anaphylaxis,[6,7,11,24–26] and include

- Cutaneous symptoms, which occur in the majority of patients, and include flushing, pruritus, urticaria, and angioedema. However, 10 to 20 percent of cases have no cutaneous manifestations.
- Respiratory symptoms, which occur in up to 70 percent of cases, and include nasal congestion and rhinorrhea, throat pruritus and laryngeal edema, choking, wheeze, cough and dyspnea.
- Gastrointestinal symptoms, which occur in up to 40 percent of cases, and include cramping, abdominal pain, nausea, emesis, and diarrhea.
- Cardiovascular symptoms, which occur in up to 35 percent of cases, and include dizziness, tachycardia, hypotension and collapse.
- Other symptoms, which may include anxiety, mental confusion, lethargy, and seizures.

Any of these symptoms may culminate in death.

6.1.4 TIME COURSE

Food-induced anaphylaxis is typically characterized by a defined exposure to a food allergen that is followed by a rapid onset and evolution of symptoms over minutes to several hours. Deaths from food-induced anaphylaxis have been reported within

30 minutes to 2 hours of exposure[27–29] and usually result from respiratory compromise.[11] Food-induced anaphylaxis can also have a milder course and resolve spontaneously, most likely due to endogenous production of vasoconstrictors (e.g., epinephrine, endothelin, angiotensin II and others).[25,30,31]

The time course of anaphylaxis may fall into three potential reaction courses: uniphasic, biphasic, and protracted.

- Uniphasic reactions occur immediately after exposure and resolve with or without treatment within the first minutes to hours, and then do not recur during that anaphylaxis episode.
- Biphasic reactions are defined as a recurrence of symptoms that develops after apparent resolution of the initial reaction. Biphasic reactions have been reported to occur in 1 to 20 percent of anaphylaxis episodes and typically occur about 8 hours after the first reaction, although recurrences have been reported up to 72 hours later.[29,32,33]
- Protracted reactions are defined as any anaphylaxis episode that lasts for hours or days following the initial reaction.[29]

Fatalities associated with food-induced anaphylaxis occur and are most commonly associated with peanut or tree nut ingestion.[27–29] Such fatalities are associated with delayed use or lack of proper epinephrine dosing. The highest risk groups for fatal anaphylaxis associated with food ingestion are

- Adolescents and young adults
- Individuals with known food allergy and with a prior history of anaphylaxis
- Individuals with asthma, especially those with poor control (although fatal reactions may occur even in individuals with mild asthma)
- Individuals without ready access to epinephrine[27–29]

6.1.5 CO-MORBID DISEASES AND FACTORS THAT INCREASE THE RISK OF ANAPHYLAXIS TO FOODS

Co-morbidities may affect symptom severity and treatment response in patients with food-induced anaphylaxis.[25,26,30,34]

- Asthma is the most important risk factors for a poor outcome. Persistent asthma, especially if not optimally controlled, is an important risk factor for death from anaphylaxis, especially in adolescents and young adults.[27–29,35,36]
- Cardiovascular disease is also an important risk factor for death from anaphylaxis, especially in middle-aged and older individuals.[37]
- Other disorders, such as mastocytosis, chronic lung disease (chronic obstructive pulmonary disease and recurrent pneumonia), and anatomic airway obstruction (e.g., airway hemangiomas, laryngotracheomalacia), may also increase risk.

Certain medications may also affect symptom severity and treatment response in patients with food-induced anaphylaxis.

- Beta-adrenergic antagonists may decrease the response to epinephrine therapy in patients undergoing anaphylaxis.
- Angiotensin-converting enzyme inhibitors and, to a lesser extent, angiotensin II receptor blockers, may interfere with endogenous compensatory mechanisms, resulting in more severe or prolonged symptoms.[38]
- Alpha-adrenergic blockers may decrease the effects of endogenous or exogenous epinephrine at alpha-adrenergic receptors, rendering patients less responsive to epinephrine.[39]

6.1.6 OTHER DISEASES ASSOCIATED WITH ACUTE REACTIONS TO FOOD

Several other food allergy disorders, described in detail in Sections 2, 3, and 4, may have acute symptoms after food ingestion.

- Some disorders share IgE-mediated mechanisms such as localized urticaria or angioedema, generalized flushing, oral allergy syndrome, and food-dependent, exercise-induced anaphylaxis and may progress to life-threatening anaphylaxis.
- Others are non-IgE-mediated disorders such as food protein-induced enterocolitis syndrome (FPIES) and allergic proctocolitis that may present with acute, repetitive gastrointestinal symptoms. In particular, FPIES may be confused with anaphylaxis because patients, minutes to hours after food or formula ingestion, often develop repetitive emesis in association with pallor, diarrhea, lethargy, and hypotension due to massive intravascular fluid shifts. Patients with FPIES require treatment via aggressive fluid resuscitation and typically do not respond to epinephrine, in contrast to patients with acute reactions due to IgE-mediated disease.

6.1.7 LABORATORY TESTING

Testing is of limited value in the acute setting. The diagnosis of food-induced anaphylaxis may be supported by tests that assess for sensitization to the suspect food allergen. However, the diagnosis is rarely supported by tests that document elevated mast cell and basophil mediators, including plasma histamine and serum or plasma total tryptase.[40–44] The use of these assays to diagnose food-induced anaphylaxis is unrealistic[42,43,45,46] because histamine is very labile and requires special handling of samples for processing. Tryptase lacks specificity and is not elevated in food-induced anaphylaxis. However, in the case of suspected anaphylaxis, elevated serum tryptase or urinary histamine levels may be very useful to confirm the diagnosis of anaphylaxis (or possibly systemic mastocytosis), but may not be indicative of a food-induced reaction. A negative tryptase finding also does not rule out food-induced anaphylaxis.

Epicutaneous prick skin testing and serum allergen-specific IgE testing (e.g., ImmunoCAP) may provide information regarding a specific food allergy (see Section 4, but do not yield information about the cause of or risk for anaphylaxis. Rather, these tests may be used as adjuncts to evaluate for allergen sensitization, while other tests (such as double-blind placebo-controlled food challenge) are useful to determine clinical allergy

(see Section 4). Correlation of testing with timing of ingestion and associated reaction, symptom profile, and response to therapy are important to make the definitive diagnosis. Additionally, there are no tests available to predict severity of IgE-mediated reactions.

6.2 TREATMENT OF ACUTE, LIFE-THREATENING, IGE-MEDIATED FOOD ALLERGIC REACTIONS

Guideline 44: The EP recommends that treatment for food-induced anaphylaxis should focus on the following:

- Prompt and rapid treatment after onset of symptoms (see Table 6.1 for pharmacologic treatment in an outpatient or hospital setting)
- Intramuscular (IM) epinephrine as first-line therapy
- Other treatments, which are adjunctive to epinephrine dosing

Rationale: Evidence supports the implementation of rapid response and treatment for food-induced anaphylaxis and the use of IM epinephrine as first-line therapy.
Balance of benefits and harms: The benefits of appropriate treatment for anaphylaxis begin with IM epinephrine injection. Benefits of epinephrine treatment far outweigh the risks of unnecessary dosing. Delays in instituting therapy with epinephrine are associated with risks of death and morbidity.
Quality of evidence: Moderate
Contribution of expert opinion to the recommendation: Significant

Table 6.1: Summary of Pharmacological Management of Food-induced Anaphylaxis in Outpatient and Hospital Settings

Drug (route)	Dose	Maximum dose	Outpatient, first line	Outpatient, adjunctive	Hospital, first line	Hospital, adjunctive
Epinephrine autoinjector (IM)	0.15 mg (For individuals 10–25kg)	-	√	-	√	-
Epinephrine autoinjector (IM)	0.3 mg (For individuals > 25kg)	-	√	-	√	-
Epinephrine IM (1:1000)	0.01 mg/kg	0.3 mg	√	-	√	-
Albuterol (Inhaler or nebulizer)	Metered-dose, every 20 minutes	-	-	√	-	√
Diphenhydramine (IV or oral)	1–2 mg/kg	50 mg	-	√	-	√
Vasopressors	Titrate to effect	-	-	-	-	√
Glucagon	5–15 μg/minute	-	-	-	-	√
Ranitidine (IV or oral)	1–2 mg/kg	75–150 mg	-	-	-	√
Prednisone (oral) or methylprednisolone (IV)	1 mg/kg	60–80 mg	-	-	-	√

As in all anaphylaxis, prompt assessment and treatment are critical for food-induced anaphylaxis events. Failure to respond promptly can result in rapid demise and death within 30–60 minutes.[21,28,29,35–37,47]

The cornerstones of initial management should begin with the following **concurrent** steps[48]

- Elimination of additional allergen exposure
- Call for help (summon a resuscitation team in the hospital setting, call 911 or an equivalent service in the community setting) although attempts to summons help should not delay use of epinephrine
- IM injection of epinephrine

These actions should be quickly followed by these additional steps[49–52]

- Place the patient in the supine position, with the lower extremities elevated (if tolerated)
- Provide supplemental oxygen
- Administer intravenous (IV) fluid (volume resuscitation)
- Administer epinephrine as soon as possible once anaphylaxis is recognized, and transport the patient to the nearest emergency facility. Delayed administration of epinephrine has been implicated in contributing to fatalities[27–29,46]

In a study of 13 fatal or near-fatal food-induced anaphylactic reactions in children, six of the seven children who survived received epinephrine within 30 minutes of ingesting the food, whereas only two of the six children who died received epinephrine within the first hour.[29] Similar findings have continued in ongoing reports of fatal anaphylaxis using the food allergy anaphylaxis registry.[27,28] Epinephrine, therefore, should be available at all times to patients at risk. A recent study in schools also highlights the fact that children with food allergy often do not have ready access to epinephrine at school, further placing them at increased risk.[53]

6.2.1 PHARMACOLOGIC TREATMENT

Pharmacologic treatment of food-induced anaphylaxis is based on extrapolation from therapies used in cardiac arrest and asthma, from uncontrolled human trials of anaphylaxis during insect sting challenges, and from studies of anaphylaxis in animal models.[2] Randomized, controlled studies that meet current standards have not been performed for any therapeutic interventions during actual anaphylaxis in humans. Placebo-controlled trials for epinephrine use have not been performed during anaphylaxis and will likely never be performed due to ethical considerations in a disease that can kill within minutes and requires prompt intervention.[54]

The evidence base for the pharmacologic management of an acute anaphylaxis episode has been extensively studied in three Cochrane collaborative reviews.[55–57] From the literature reviewed, the EP did not identify any randomized controlled trials (RCTs) that met current standards. However, these reviews highlight that epinephrine has been relatively well-investigated in terms of

- Observational studies
- RCTs in patients not experiencing anaphylaxis at the time of administration
- Epidemiologic studies

- Fatality studies
- *In vitro* studies and studies in animal models

Experts in the field agree that epinephrine is the only first-line treatment for anaphylaxis. There is no substitute for epinephrine, thus all other treatments are adjunctive. Antihistamines (both H1 and H2 blockers), corticosteroids, or both are commonly used in the treatment of anaphylaxis, but there are little or no data demonstrating their functional role or effectiveness.

In summary: The use of antihistamines is the most common reason reported for not using epinephrine[31] and may place the patient at significantly increased risk for progression toward a life-threatening reaction.

Table 6.2 briefly summarizes the pharmacologic management of anaphylaxis in outpatient and hospital settings. A more complete summary of the pharmacologic management of anaphylaxis is given below.

Table 6.2: Summary of the Pharmacologic Management of Anaphylaxis (adapted[49])

In the outpatient setting

- First line treatment
  - Epinephrine Autoinjector
    - 10 to 25 kg: 0.15 mg epinephrine IM (anterior-lateral thigh)
    - >25 kg: 0.3 mg epinephrine IM (anterior-lateral thigh)
  - Epinephrine (1:1000), 0.01 mg/kg per dose; maximum dose, 0.3 mg per dose IM (anterior-lateral thigh)
- Adjunctive treatment
  - Albuterol (β_2-agonist) metered-dose inhaler or nebulized solution every 20 min or continuously as needed
  - Diphenhydramine (H_1 antagonist), 1 to 2 mg/kg per dose; maximum dose, 50 mg IV or oral (oral liquid is more readily absorbed than tablets)
  - Oxygen therapy
  - Intravenous fluids in large volumes if patients present with orthostasis, hypotension or incomplete response to IM epinephrine
  - Patient positioning, recumbent position with lower extremities elevated

Hospital-based

- First line treatment
  - Epinephrine IM as above, consider intermittent IV epinephrine boluses vs. continuous epinephrine infusion for persistent hypotension; alternative is endotracheal epinephrine
- Adjunctive treatment
  - Vasopresssors for refractory hypotension, titrate to effect
  - Glucagon for refractory hypotension 5 to 15 µg/min, titrate to effect
  - Albuterol (β_2-agonist) nebulized solution or metered dose inhaler every 20 min or continuous as needed

- Diphenhydramine (H_1 antagonist), 1 to 2 mg/kg per dose; maximum dose, 50 mg oral, IV, and IM (if not already given)
- Ranitidine (H_2 antagonist),1 to 2 mg/kg per dose; maximum dose, 75 to 150 mg oral and IV
- Corticosteroids: prednisone at 1 mg/kg with a maximum dose of 60 to 80 mg oral or methylprednisolone at 1 mg/kg with a maximum dose of 60 to 80 mg IV
- Oxygen therapy
- Intravenous fluids in large volumes if patients present with orthostasis, hypotension or incomplete response to IM epinephrine
- Patient positioning, recumbent position with lower extremities elevated

Discharge therapy

- First line treatment:
  - Epinephrine autoinjector prescription and instructions
  - Education on avoidance of allergen
  - Follow-up with primary care physician
  - Consider referral to an allergist
- Adjunctive treatment:
  - Diphenhydramine (H_1 antagonist) every 6 h for 48 to72 hr
  - Ranitidine (H_2 antagonist), twice daily for 48 to 72 hr
  - Prednisone (corticosteroid) twice daily for 48 to 72 hr

6.2.1.1 Epinephrine—First Line Treatment

Epinephrine is the drug of choice for anaphylaxis and should be administered as **first-line therapy**. The pharmacologic actions of this agent address the pathophysiologic changes that occur in anaphylaxis better than any other single drug. Failure to administer epinephrine early in the course of treatment has been repeatedly implicated in anaphylaxis fatalities.[1,6,8,27–29,58] Despite this fact, physicians often fail to prescribe epinephrine, and emergency responses can vary by region.[2,15,31,59,60]

The therapeutic actions of epinephrine, which encompass a broad range of effects germane to the mechanisms of anaphylaxis, include the following[52]

- Increased vasoconstriction, increased peripheral vascular resistance, and decreased mucosal edema via alpha-1adrenergic agonist receptor effects
- Increased inotropy and increased chronotropy via beta-1 adrenergic receptor agonist effects
- Bronchodilation and decreased release of mediators of inflammation from mast cells and basophils via beta-2 adrenergic receptor agonist effects.

Epinephrine has a narrow toxic-therapeutic index (risk-to-benefit ratio). In therapeutic doses and by any route, epinephrine frequently causes transient adverse effects in individuals of all ages. These include anxiety, fear, restlessness, headache, dizziness, palpitations, pallor, and tremor.[52] Rarely, and especially after overdose, it may lead to

ventricular arrhythmias, angina, myocardial infarction, pulmonary edema, sudden sharp increase in BP, and intracranial hemorrhage.[52]

Epinephrine has an onset of action within minutes but is rapidly metabolized. Therefore, the effect is often short-lived and repeated doses may be necessary.[31,61,62] Epinephrine can be delivered through a variety of routes including IM, IV, and endotracheal. Subcutaneous injection is of limited benefit when compared to IM dosing[51] and should not be used.

- **IM epinephrine** is recommended over subcutaneous injection because it provides more rapid plasma and tissue concentrations of epinephrine.[7,35,51] The dose should be given intramuscularly into the anterolateral thigh in the vastus lateralis muscle. When using an epinephrine autoinjector (e.g., EpiPen® or Twinject®), children weighing less than 25 kg should receive the 0.15 mg pediatric dose.[63] Children over 25 kg through adults should use the 0.3 mg dose. The needle used in autoinjectors in adults should be of adequate length to reach the muscle beneath the subcutaneous adipose tissue over the vastus lateralis muscle (e.g., 1.5 inches in a normal adult). IM injection into the thigh may be impossible in overweight or obese individuals, especially women who have higher subcutaneous fat tissue.[64,65] In the circumstance of inadequate IM dosing, subcutaneous dosing will provide some benefit but will be less effective than IM dosing; therefore, alternatives may need to be considered, such as deltoid site delivery or needle/syringe dosing of aqueous epinephrine.
- **IV epinephrine** is recommended for patients who do not respond to an initial (or repeated) IM injection of epinephrine and whose fluid resuscitation may not be adequately perfusing muscle tissues.[25]
- **Endotracheal epinephrine** can be delivered if IV access cannot be obtained immediately. The efficacy of this delivery method is based upon small series of patients experiencing cardiac arrest.[26] Sublingual epinephrine is in early development stages and not yet available for clinical use.[66]
- **Repeated dosing of epinephrine** may be required if a patient responds poorly to the initial dose or has ongoing or progressive symptoms despite initial dosing. Several reports of patients receiving epinephrine for food and other allergen anaphylaxis or food-induced anaphylaxis[61,62] note that approximately 10 to 20 percent of individuals who receive epinephrine will require more than one dose before recovery of symptoms. In many of the cases, the subsequent doses of epinephrine were given less than15 minutes from the first dose (some more than 1 hour) despite recommendations to repeat dosing as frequently as every 5 to 15 minutes. Optimal dosing interval for repeated dosing has not been studied prospectively.

6.2.1.2 Adjunctive Treatment

- **H1 Antihistamines.** In contrast to epinephrine, there is very limited scientific evidence to support the use of H1 antihistamines in the emergency treatment of anaphylaxis.[4] H1 antihistamines are useful only for relieving itching and urticaria. They do not relieve stridor, shortness of breath, wheezing, gastrointestinal

symptoms, or shock. Therefore, they should be considered adjunctive therapy and should not be substituted for epinephrine.[17,27–29,47,55,67]

The first-generation H1 antihistamines are most commonly administered due to their availability for IV and oral dosing when compared to second-generation antihistamines. Both have onset of action within 20 to 60 minutes, but first-generation antihistamines have a shorter duration of action, lasting 4 to 7 hours compared to 12 to 24 hours for second-generation antihistamines. Additionally, sedation and psychomotor impairment must be recognized as side effects of the first-generation antihistamine medications that may decrease cognitive awareness of symptoms.[55,67]

- **Corticosteroids.** Very little information is available to support or refute the use of corticosteroids for the treatment of acute anaphylaxis. However, their empiric use is prevalent and supported by many clinicians. Corticosteroids are not helpful in the treatment of acute anaphylaxis due to their slow onset of action (4 to 6 hr). These agents are often given because of their anti-inflammatory properties that benefit allergic and inflammatory disease and also because they may help to prevent the biphasic or protracted reactions, which occur in up to 20 percent of individuals.[1,33] Treatment should be stopped within 2 to 3 days, since all biphasic reactions reported to date have occurred within 3 days.[33]
- **H2 Antihistamines.** There is minimal evidence to support the use of H2 antihistamines in the emergency treatment of anaphylaxis.[69] Some clinicians use these medications as empiric therapy under the premise that they further bind histamine receptor isoforms. However, studies to support this idea are lacking.
- **Bronchodilator medications.** For the treatment of bronchospasm not responsive to IM epinephrine, inhaled bronchodilators, such as albuterol, should be used as needed and should be considered to be adjunctive therapy to epinephrine administration. Albuterol does not relieve airway edema and should not be substituted for IM epinephrine dosing in the treatment of anaphylaxis. In most emergency care settings, nebulized therapy may be more practical than metered-dose inhalers (with spacers) for patients with respiratory distress, but metered-dose inhalers can also be helpful when the respiratory distress is mild or when nebulized therapy is not available. Moreover, the effectiveness of albuterol delivery via nebulizer versus metered-dose inhaler (with spacer) remains uncertain for patients with severe respiratory distress. Therefore, the EP recommends albuterol administration via nebulizer (if available) in this setting.
- **Oxygen therapy.** Oxygen should be administered initially to all patients experiencing anaphylaxis, especially those with evidence of hypoxia or respiratory distress. Not only does supplemental oxygen help with optimization of oxygen delivery and organ perfusion, but it also serves to help with bronchodilation.[24]
- **Intravenous Fluids.** Many patients with anaphylaxis require IV fluids. Massive fluid shifts can occur rapidly in anaphylaxis due to increased vascular permeability, with transfer of up to 35 percent of the intravascular volume into the extravascular space within minutes.[40] Any patient who does not respond promptly and completely to injected epinephrine should be assumed to have **intravascular**

volume depletion causing persistent hypotension despite maximum vasoconstriction. These patients should receive large volume fluid resuscitation, with normal saline being the preferred treatment. Larger volume fluid resuscitation should be initiated immediately in patients who present with orthostasis, hypotension, or incomplete response to IM epinephrine.[24]

- **Vasopressors.** Patients who have persistent hypotension despite the administration of epinephrine and IV fluids should receive vasopressor medications titrated to the desired effect of restoring blood pressure. Due to the narrow benefit-to-risk ratio of these medications,[70] patients requiring vasopressors should be transferred to a hospital setting for acute care. There is no compelling evidence to support one vasopressor over another in this clinical scenario.
- **Patient positioning.** The patient should be placed in the recumbent position with the lower extremities elevated to maximize perfusion of vital organs. This also helps prevent "empty ventricle syndrome," in which severe hypotension leads to inadequate cardiac filling and electrical cardiac activity without a pulse.[71] Individuals with respiratory distress or vomiting may not tolerate the recumbent position.
- **Medications and confounding factors that may affect treatment response.** Concurrent administration of certain medications may affect the patient's ability to respond to both treatment and compensatory physiologic responses. Beta-adrenergic antagonists, administered orally, parenterally, or topically (e.g., eye drops) may decrease the effects of endogenous or exogenous epinephrine at beta-adrenergic receptors and render patients less responsive to epinephrine.[72] Patients receiving beta-blockers may be resistant to treatment with epinephrine and can develop refractory hypotension and bradycardia. Glucagon should be administered in this setting because it has inotropic and chronotropic effects that are not mediated through beta-receptors.[60] A dose of 1 to 5 mg in adults (in children, 20 to 30 μg/kg, to a maximum of 1 mg) administered intravenously over 5 minutes is recommended, which may be repeated or followed by an infusion of 5 to 15 μg/minute.[26] Rapid administration of glucagon can induce vomiting.
- **Refractory anaphylaxis: patients without effective epinephrine response.** There are no published prospective studies on the optimal management of refractory anaphylactic shock. Repeated use of epinephrine, as well as intravenous fluids, corticosteroids, and vasopressor agents may be needed.[24] Prompt transfer to an acute-care facility and intensive-care unit for treatment and monitoring is essential.
- **Possible risks of acute therapy for anaphylaxis.** There are no absolute contraindications to epinephrine use in anaphylaxis.[24,43] However, there are subgroups of patients who might theoretically be at higher risk for adverse effects during epinephrine therapy. Because the risk of death or serious disability from anaphylaxis itself usually outweighs other concerns,[24,43] existing evidence clearly favors the benefit of epinephrine administration in most situations. Some level of decision-making regarding the risk/benefit ratio for the patient may be warranted, and especially for patients
    - With cardiovascular diseases, and who are reluctant to receive epinephrine due to fear of adverse cardiac effects. These patients should be made aware

that myocardial ischemia and dysrhythmias can occur in untreated anaphylaxis.[40]
    - Receiving monoamine oxidase inhibitors (which block epinephrine metabolism), or tricyclic antidepressants (which prolong epinephrine duration of action)
    - Receiving stimulant medications (e.g., amphetamines or methylphenidate used in the treatment of attention-deficit-hyperactivity disorder) or abusing cocaine
    - With certain preexisting conditions, such as recent intracranial surgery, aortic aneurysm, uncontrolled hyperthyroidism or hypertension; and
    - Who are pregnant, due to possible risks of ischemic effects on the unborn fetus.

- **Treatment to prevent biphasic or protracted food allergic reactions.** Very little information exists that defines the mechanism of biphasic or protracted allergic reactions. Similarly, little information exists to support specific therapy to prevent biphasic or protracted food-induced allergic reactions. In general, induction and recruitment of inflammatory cells and release of preformed, long-acting mediators from mast cells have been implicated as mechanisms.[33] Although little data supports their use, systemic corticosteroids often are recommended medications to prevent biphasic or protracted food allergic reactions due to their anti-inflammatory properties.
- **Management of milder, acute food allergic reactions in healthcare settings.** Milder forms of allergic reactions, such as flushing, urticaria or isolated, mild angioedema, or symptoms of oral allergy syndrome can be treated with H1 and H2 antihistamine medications.[12,69] When antihistamines alone are given, ongoing observation and monitoring is warranted to ensure a lack of progression to more significant symptoms of anaphylaxis. If progression or increased severity is noted, epinephrine should be administered immediately. Additionally, if there is a history of a prior severe allergic reaction, epinephrine should be administered promptly and earlier in the course (e.g., at the onset of even mild symptoms).

6.3 MANAGEMENT FOLLOWING FOOD-INDUCED ANAPHYLAXIS

Guideline 45: The EP recommends that the management of food-induced anaphylaxis should focus on the following

- Dosing with IM epinephrine followed by transfer to an emergency facility for observation and possible further treatment
- Observation for 4 to 6 hours or longer based on severity of the reaction
- Education for patient and family for
    - Trigger avoidance
    - Early recognition of signs and symptoms
    - Anaphylaxis Emergency Action Plan implementation
    - Appropriate IM epinephrine administration
    - Education on medical identification jewelry or an Anaphylaxis Wallet Card
- Epinephrine autoinjector prescription and training provided at the time of discharge

- Follow-up appointment with primary healthcare provider, (after the food-induced anaphylactic reaction) with consideration for additional follow-up with an allergist

Rationale: Despite the lack of evidence, the EP recommends close monitoring, scheduled follow-up, and patient education for effective management following anaphylaxis.
Balance of benefits and harms: The benefits of appropriate management following food-induced anaphylaxis should serve to further protect the patient through long-term follow-up, care and education with the benefit of preventing subsequent events. The potential harm is minimal if appropriate education is employed.
Quality of evidence: Low
Contribution of expert opinion to the recommendation: Significant

6.3.1 OBSERVATION PERIOD

There is no consensus in the literature regarding the optimal amount of time that a patient, who has been successfully treated for anaphylaxis, should be observed prior to discharge. All patients that receive epinephrine for food-induced anaphylaxis should proceed to an emergency facility for observation and possibly additional treatment. A reasonable length of time to consider for observation is 4 to 6 hours in most patients who have experienced anaphylaxis, with prolonged observation times or hospital admission for patients with severe or refractory symptoms.[9,26]

6.3.2 DISCHARGE PLAN FOLLOWING TREATMENT FOR FOOD-INDUCED ANAPHYLAXIS

All patients who have experienced anaphylaxis should be sent home with the following:

- Anaphylaxis Emergency Action Plan
- Epinephrine auto-injector(s) (or two-pack prescription)
- Plan for monitoring auto-injector expiration dates
- Plan for arranging further evaluation, and
- Printed information about anaphylaxis and its treatment[31]

6.3.2.1 Anaphylaxis Emergency Action Plan

Patients should be given a written Anaphylaxis Emergency Action Plan that contains information about self-injection of epinephrine prior to discharge[25,73] (see Sample Action Plan in Appendix C). Patients should be instructed on the value of medic-alert jewelry to easily identify themselves as a patient with anaphylaxis potential and their food allergen triggers.

6.3.2.2 Epinephrine auto-injector (or two-pack prescription)

All patients experiencing anaphylaxis should be provided directly with an epinephrine auto-injector or, if this is not possible, with a prescription (recommend prescription is for an epinephrine two-pack), and advised to fill it immediately.

Other patients that should be given an epinephrine autoinjector include

- Patients with a history of a prior systemic allergic reaction
- Patients with food allergy and asthma
- Patients with a known food allergy to peanut, tree nut, fish, and crustacean shellfish (i.e., allergens known to be associated with more fatal and near-fatal allergic reactions)

In addition, consideration should be given to prescribing an epinephrine autoinjector to all food allergic patients having IgE-mediated reactions because of the inability of the patient to predict the severity of any subsequent reactions.

Instructions in the proper use of epinephrine autoinjectors should be reviewed verbally and accompanied by a written Anaphylaxis Emergency Action Plan. Special care should be taken to explain the importance of carrying epinephrine at all times and on advising the patient to make sure that family and friends are aware of the risks of anaphylaxis, the patient's triggers, and how to administer epinephrine. Where allowed by state law, students should be advised to carry their epinephrine auto-injector to and from school.

6.3.2.3 Plan for monitoring auto-injector expiration dates

Patients and family members should be advised to regularly check the epinephrine auto-injector expiration dates. Ideally, the prescribing physician's office should notify patients (or the family members of patients who are minors) by telephone and/or mail that their auto-injector will soon reach its expiration date and that the prescription should be renewed.

6.3.2.4 Plan for arranging further evaluation

Advice should be provided to the patient regarding follow-up with his or her primary care provider within 1 to 2 weeks after a food-induced anaphylaxis event. Additional information may be needed about obtaining a referral to an allergist or about how to seek consultation directly with an allergist for testing, diagnosis, and ongoing management of the allergy. Direct communication between the treating clinician and the primary care provider is recommended in order to ensure that appropriate follow-up is attained.

6.3.2.5 Printed information about anaphylaxis and its treatment

The emergency doctor, treating physician, or healthcare provider should provide the patient who has been treated for anaphylaxis and is subsequently leaving the emergency department or hospital with printed information about anaphylaxis and its treatment.[74] The mnemonic "SAFE" has been developed to remind clinicians of the four basic action steps suggested for these patients.[74] The SAFE (**S**eek support, **A**llergen identification and avoidance, **F**ollow-up with specialty care; **E**pinephrine for emergencies) counseling is outlined below and has been incorporated into printable patient information materials.

- **Seek support –** the healthcare provider should advise patients that
  - They have experienced anaphylaxis, which is a life-threatening condition.

- Symptoms of the current episode may recur up to three days after the initial onset of symptoms.
- They are at risk for repeat episodes of anaphylaxis in the future.
- At the first sign of recurrence of symptoms, the patient should give himself/herself epinephrine and then immediately call an ambulance or get to the nearest emergency facility.

- **Allergen identification and avoidance** − the healthcare provider should
  - Make efforts to identify the patient's trigger (through history and with follow-up for further testing) before the patient is discharged.
  - Emphasize the importance of subsequent testing to determine and verify the trigger, so that it can be successfully avoided in the future.
- **Follow-up with specialty care** – the healthcare provider should
  - Advise the patient to follow-up with their primary care provider and that they may benefit from subspecialty allergy evaluation.
- **Epinephrine for emergencies** – the healthcare provider should
  - Provide the patient with self-injectable epinephrine or a prescription, and educate the patient about its use prior to discharge.
  - Advise the patient and/or family members to routinely check the expiration date of the auto-injector.

Other sources of accurate patient information, accessible through the Internet, include the American Academy of Allergy, Asthma and Immunology (www.aaaai.org) and the American College of Allergy, Asthma and Immunology (www.acaai.org).

6.4 KNOWLEDGE GAPS

Due to a lack of controlled studies in the area of food-induced anaphylaxis management, significant knowledge gaps exist in several areas including

- The role of a variety of medications (e.g., corticosteroids, antihistamines, others) in acute management and prevention of follow-up reactions.
- The true incidence of biphasic and protracted reactions related to food-induced anaphylaxis and appropriate medical management to prevent or effectively treat these reactions.
- The relative benefits of certain alternative routes of epinephrine administration (e.g., sublingual).
- The most effective methods for appropriate education of patients, families, healthcare providers and others to most effectively protect patients at risk for anaphylaxis related to food proteins.

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*** Supplementary document identified by the EP**

APPENDIX A: COORDINATING COMMITTEE MEMBER ORGANIZATIONS

Agency for Healthcare Research and Quality (AHRQ)
Allergy and Asthma Network Mothers of Asthmatics (AANMA)
American Academy of Allergy, Asthma and Immunology (AAAAI)
American Academy of Dermatology (AAD)
American Academy of Emergency Medicine (AAEM)
American Academy of Pediatrics (AAP)
American Academy of Physician Assistants (AAPA)
American College of Allergy, Asthma and Immunology (ACAAI)
American College of Emergency Physicians (ACEP)
American College of Gastroenterology (ACG)
American College of Physicians (ACP)
American Dietetic Association (ADA)
American Nurses Association (ANA)
American Partnership for Eosinophilic Disorders (APFED)
American Society for Nutrition (ASN)
American Thoracic Society (ATS)
Asthma and Allergy Foundation of America (AAFA)
Centers for Disease Control and Prevention (CDC)
European Academy of Allergy and Clinical Immunology (EAACI)
Food Allergy and Anaphylaxis Network (FAAN)
Food Allergy Initiative (FAI)
Inflammatory Skin Disease Institute (ISDI)
National Association of School Nurses (NASN)
National Heart, Lung and Blood Institute (NHLBI)
National Institute of Allergy and Infectious Disease (NIAID)
National Institute of Child Health and Human Development (NICHD)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Institute of Nursing Research (NINR)
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)
Society for Pediatric Dermatology (SPD)
Society of Pediatric Nurses (SPN)
United States Department of Agriculture (USDA)
United States Environmental Protection Agency (EPA)

APPENDIX B: EXPERT PANEL MEMBERS

Chair:

Joshua A. Boyce, MD
Associate Professor of Medicine
Harvard Medical School
Specialty: Allergy, Pediatric Pulmonology

Panelists:

S. Hasan Arshad, MBBS, MRCP, DM, FRCP
Reader in Allergy, Infection, Inflammation and Repair
University of Southampton
Specialty: Allergy/Epidemiology

Amal Assa'ad, MD
Professor, Director, Allergy & Immunology fellowship
Associate Director, Division of Allergy & Immunology
Cincinnati Children's Hospital Medical Center
Specialty: Allergy/Pediatrics

Sami L. Bahna, MD, DrPH
Professor of Pediatrics & Medicine, Chief of Allergy & Immunology Section, Director of Allergy & Immunology Training Program
Louisiana State University Health Sciences Center
Specialty: Allergy

Lisa A. Beck, MD
Associate Professor of Dermatology, Director of Translational Research
University of Rochester Medical Center
Specialty: Dermatology

A. Wesley Burks, MD
Professor, Department of Pediatrics
Duke University
Specialty: Allergy/Pediatrics

Carol Byrd-Bredbenner PhD, RD, FADA
Professor of Nutrition/Extension Specialist
Rutgers, The State University of New Jersey
Specialty: Nutrition/Education

Carlos A. Camargo, MD, DrPH
Director, EMNet Coordinating Center
Massachusetts General Hospital
Harvard Medical School
Specialty: Epidemiology/Emergency Medicine

Lawrence Eichenfield, MD
Professor, Department of Pediatrics and Medicine (Dermatology)
University of California, San Diego School of Medicine
Director, Children's Specialists of San Diego
Rady Children's Hospital, San Diego
Specialty: Dermatology/Pediatrics

Glenn T. Furuta, MD
Associate Professor
University of Colorado Denver, School of Medicine
Specialty: Gastroenterology/ Pediatrics

Jon M. Hanifin, MD
Professor of Dermatology
Oregon Health and Science University
Specialty: Dermatology

Carol Jones, RN, AE-C
Certified Asthma Nurse Educator & Consultant
Specialty: Nursing, Education

Stacie M. Jones, MD
Professor of Pediatrics, Chief of Allergy/Immunology
University of Arkansas for Medical Sciences and Arkansas Children's Hospital
Specialty: Allergy/Pediatrics

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Professor of Medicine
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Clinical Professor of Medicine, Division of Allergy and Immunology
Clinical Professor of Pediatrics
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Specialty: Allergy/Pediatrics

Lynda C. Schneider, MD
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Specialty: Allergy/Internal Medicine

F. Estelle R. Simons, MD
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Stephen J. Teach, MD, MPH
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Barbara P. Yawn, MD, MPH, MSc
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Olmstead Medical Center
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APPENDIX C: SAMPLE OF AN ANAPHYLAXIS EMERGENCY ACTION PLAN

NAME: _____ **AGE:** _____

ALLERGY TO:_____

Asthma: Yes (high risk for severe reaction) □ **No** □

Other health problems besides anaphylaxis:

_____

_____

Concurrent medications, if any:

_____

_____

SYMPTOMS OF ANAPHYLAXIS INCLUDE:

- MOUTH itching, swelling of lips and/or tongue
- THROAT* itching, tightness/closure, hoarseness
- SKIN itching, hives, redness, swelling
- GUT vomiting, diarrhea, cramps
- LUNG* shortness of breath, cough, wheeze
- HEART* weak pulse, dizziness, passing out

Only a few symptoms may be present. Severity of symptoms can change quickly.
*Some symptoms can be life-threatening! **ACT FAST!**

WHAT TO DO:

1. **INJECT EPINEPHRINE IN THIGH USING (check one):**

□ EpiPen Jr (0.15 mg) □ Twinject 0.15 mg
□ EpiPen (0.3 mg) □ Twinject 0.3 mg

Other medication/dose/route:
_____

IMPORTANT: ASTHMA PUFFERS AND/OR ANTIHISTAMINES CAN'T BE DEPENDED ON IN ANAPHYLAXIS!

2. CALL 911 or RESCUE SQUAD (BEFORE CALLING CONTACTS)!

3. EMERGENCY CONTACTS

#1: home _____ work _____ cell _____
#2: home _____ work _____ cell _____
#3: home _____ work _____ cell _____

DO NOT HESITATE TO GIVE EPINEPHRINE!

COMMENTS:
_____
_____

_____ _____

Doctor's Signature/Date Parent's Signature (for individuals under age 18 yrs)/Date

Adapted from J Allergy Clin Immunol 1998;102:173–176 and J Allergy Clin Immunol 2006;117:367–377